National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 10 Highlights
Old Post Office, M09
1100 Pennsylvania Avenue
Washington, D.C.
June 8-11, 1998

INTRODUCTION

In opening remarks, Roger Garrett expressed appreciation for the productivity of the AEGL program on the occasion of its second anniversary. George Rusch (Chair) stated that approximately 52 chemicals to date have been addressed by the NAC/AEGL and that 12 published in the Federal Register are also being submitted to the National Academy of Science Committee of Toxicology (NAS/COT) for review. Roger Garrett indicated that the COT may meet in late July or early August for its initial review of these chemicals and the NAC/AEGL Standing Operating Procedures (SOP).

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 9 (March 10-12,1998) were reviewed and approved with minor revision to the section on nickel carbonyl (Appendix A).

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group

Ernest Falke (EPA) led discussion on the draft SOP document that was distributed prior to the NAC meeting. He emphasized that any comments received during the discussion or by June 30, 1998, would be addressed in the revision of the document. Several comments of an editorial nature were also received. There was also discussion pertaining the use of the term "ceiling" in the AEGL definitions. It was agreed that Jonathan Borak, George Rodgers, and Doan Hansen would prepare definitions/guidelines for hypersusceptible populations for inclusion in the SOP document. Jonathan Borak also emphasized that AEGLs are planning tools and not for retrospective use. If needed, SOP-specific issues can be re-opened and addressed at future meetings.

General Interest Items

- Draft Guideline for Carcinogens

  Richard Thomas led discussion on the acute exposure/carcinogenesis issue (Attachment 3). Richard stated that views regarding the carcinogenic potential of acute exposures to toxicants are equivocal. Robert Snyder cautioned that extrapolation from long-term (e.g., 2-year bioassays) does not account for the critical time factor usually required for a carcinogenic response, and that extrapolation from cancer bioassays that use a Maximum-Tolerated Dose to an acute exposure may be precarious. Editorial suggestions were also provided that included a suggestion to move the last paragraph of the write-up (regarding the acute exposure issues) to the beginning, making for a more effective introduction to the issue. Following revision of the write-up, it will be recirculated among the NAC/AEGL.

- Draft Guideline for Anesthesia

  George Rodgers discussed the basic issue of anesthesia that would be relevant to AEGL derivation (Attachment 4). These included the relationship between blood:gas partition coefficients and rate of anesthesia induction, the Minimal Alveolar Concentration (MAC),and other factors affecting anesthesia (e.g., temperature, blood chemistry, lung pathology, age, etc.). He stated that children are known to be clinically more sensitive but that quantitative data are lacking. He also explained that the precise mechanism of anesthesia is still unknown.

- Bromine Testing

  Larry Gephart circulated a copy of the correspondence to Great Lakes Chemical Corporation indicating the need for additional acute exposure toxicity data for bromine (Attachment 5). Larry informed the NAC/AEGL that a panel of industry representatives indicated that testing may be done. Consequently, Larry recommended that the deliberations on bromine AEGLs be deferred until decisions on testing or the results of new tests become available.

- Benchmark Dose

  Robert Benson provided a summary of the Benchmark Dose (BMD) methodology emphasizing that one must assess the validity and quality of the biology/toxicology data prior to application of the BMD program (Attachment 6). Robert Snyder provided his conceptual application of BMD approach to AEGLs development (Attachment 7). He also stated that the NAS/COT is currently establishing guidelines for using the BMD and that the ED_{10} is being considered as the benchmark, providing that appropriate data are available. Additionally, the NAS/COT is also currently assessing the procedures for extrapolating to lower response levels and the application of uncertainty factors (specifically, a methodology that does not simply multiply factors and that incorporates the slope of the dose-response curve).

- Tests for Sensory Irritation

  Pam Dalton gave an excellent presentation on testing of volatile chemicals that are sensory irritants. Data were presented that addressed key questions: (1) Does odor have an effect on the response ?, (2) Is there adaptation to the response, and (3) Can expectation/beliefs about the chemical influence perception of odor and irritation? The results of tests have indicated that the answer to all of these questions is yes. In such testing, involvement of the trigeminal nerve was a criterion for irritation and the slope of the irritation response was much steeper than that for the odor response. It occurs above the odor threshold but below the irritation threshold (as determined by trigeminal activation). The annoyance response tended to be perceived irritation and was more closely related to odor than to true irritation. Currently, both subjective and objective methods are being used to evaluate irritation in humans. Physiologic and biochemical endpoints will also be investigated.

- Application of AEGLs to Air Release Dispersion Model

  The application of AEGL values (specifically AEGL-2 values) in a dispersion model was presented by Ken Steinberg (Attachment 8). The model incorporates elements such as release description

and meteorologic conditions and provides information on toxic cloud footprint, greatest cloud penetration, and other factors allowing for analysis of the release scenario. For short duration releases, the lower AEGL

time points (30 min and 1 hr) were used, while for longer duration release the longer time points (4 and 8 hrs) were used. Using the chlorine AEGL values, for a 60-second release scenario, it was found that downwind cloud penetration distance was greatest for the 10-min AEGL-2 and, as expected, was less for 2-, 3-, and 60-min AEGL-2. Modeling of a 5-min hydrogen fluoride release, however, produced unexpected results.

AEGL PRIORITY CHEMICALS

Propylene Oxide, CAS No. 75-56-9

Chemical Manager: Dr. James Holler, ATSDR
Author: Dr. Claudia Troxel, ORNL

Presentations were made on behalf of the CMA Propylene Oxide (PO) Panel. Larry Andrews made a presentation summarizing the CMA Propylene Oxide Panels' concerns regarding the application of the human and animal data in the derivation of the draft AEGLs for propylene oxide (Attachments 9 and 10). Additionally, the issues of mechanistic similarity/dissimilarity of propylene oxide and ethylene oxide, and the application of uncertainty factors were discussed. Alternate AEGL values were presented with summary remarks that human data should be used and, where possible, linked to the animal data. Susan Ripple discussed the human exposure and experience data for propylene oxide (Attachment 11). The presentation focused on the use of human data for the development of AEGL values and also upon newly released sample and task duration information. Cheryl Bast provided an overview of the current draft AEGL values for propylene oxide and the data sets used in their derivation. There was also discussion regarding the flat-lining of AEGL values across time periods when contact irritation was the endpoint of concern. In deliberations on other AEGL chemicals, flat-lining was shown to be appropriate. It was the consensus of the NAC/AEGL that further deliberations on propylene oxide be deferred to the September 1998 meeting pending receipt of company reports and review of the data.

Acrolein, CAS No. 107-02-8

Chemical Manager: Dr. Robert Snyder, Rutgers University
Author: Dr. Cheryl Bast, ORNL

An overview of the derivation of draft AEGLs for acrolein was presented by Cheryl Bast (Attachment 12). Following discussions of possible AEGL values, a motion was made (Steve Barbee, seconded by Loren Koller) to accept AEGL-2 values of 0.18 ppm for 30 min and 0.1 ppm for 1, 4, and 8 hrs. The values were based upon a 1-hr exposure to 0.3 ppm and a total uncertainty factor application of 3. In the absence of data for a 30-min exposure duration, the 1-hr exposure of 0.3 ppm was adjusted to 0.18 ppm by temporal scaling to attain the 30-min exposure value. The 4- and 8-hr values were then flat-lined based upon the 1-hr value of 0.1 ppm (0.3 ppm adjusted by a total UF of 3). These values were accepted [YES: 20; NO: 8]. A motion was made by Robert Benson to accept the AEGL-1 value as presented in the Technical Support Document. The motion, seconded by Richard Thomas, passed unanimously. Following discussion on the effect if varying the temporal extrapolation exponent, n, a motion was made by Robert Benson to accept the AEGL-3 values of 2.5, 1.4, 0.48, and 0.27 for 30-minute, 1, 4, and 8 hrs, respectively (UP = 10; n = 1.2).

The 30-min and 1-hr values were based upon a 1-hr NOEL of 14 ppm for lethality while the 4- and 8-hr AEGL-3 values were based upon a 4-hr NOEL of 4.8 ppm for lethality. The motion, seconded

by George Rodgers, passed unanimously (Appendix B).

SUMMARY OF PROPOSED AEGL VALUES FOR ACROLEIN					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	eye irritation, annoyance, discomfort in humans
AEGL-2	0.18 ppm 0.41 mg/^{3}	0.10 ppm 0.23 mg/m^3	0.10 ppm 0.23 mg/m^3	0.10 ppm 0.23 mg/m^3	10% decrease in respiratory rate in humans
AEGL-3	2.5 ppm 5.7 mg/m^3	1.4 ppm 3.2 mg/m^3	0.48 ppm 1.1 mg/m^3	0.27 ppm 0.62 mg/m^3	NOEL for death in rats

Peracetic acid, CAS No. 79-21-0

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Kowetha Davidson, ORNL

The issue of the chemical composition of peracetic acid (hydrogen peroxide, acetic acid and sulfuric acid) and the changeable nature of the relative concentrations of these component was considered to be a relevant issue of concern regarding the development of AEGL value for this chemical (Attachment 13). Following discussion on uncertainty factor application, the AEGL-3 values of 9.6 ppm, 4.8 ppm, 2.6 ppm, and 1.9 ppm were passed [YES: 24, NO: 1, ABSTAIN: 0]; motion made by Ernest Falke (seconded by George Rodgers) for the 30-min, 1-, 4-, and 8-hr time periods, respectively. The 30-min AEGL-3 values were based upon a 30-min. nonlethal exposure of 96 ppm, while the 1-hr value was based upon a 1-hr nonlethal exposure of 48 ppm. The 4-hr and 8-hr values were scaled from the 1-hr value using an exponent of 2.2. The AEGL-2 values were based upon an estimated irritation threshold in humans of 0.5 ppm, 1.5 ppm caused slight discomfort and 2 ppm induced severe irritation). An uncertainty factor of 3 (protection of sensitive individuals) was applied to the 1.5 ppm and the resulting 0.5 ppm value was proposed for all time periods. A motion made by Robert Snyder and seconded by George Rodgers to accept these values was approved [YES: 22, NO: 1, ABSTAIN: 0]. For the AEGL-1 values, discussion focused on 0.5 ppm causing mild discomfort in human subjects. Application of an uncertainty factor of 3 for protection of sensitive individuals resulted in proposed AEGL-1 values of 0.17 ppm for all time periods. Following a motion made by Larry Gephart (seconded by Thomas Hornshaw), these values were accepted by the NAC/AEGL [YES: 21, NO: 4, ABSTAIN: 0]. (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR PERACETIC ACID					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**

AEGL-1	0.17 ppm 0.53 mg/m^3	0.17 ppm 0.53 mg/m^3	0.17 ppm 0.53 mg/m^3	0.17ppm 0.53 mg/m^3	Threshold for irritation in human subjects
AEGL-2	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	1.5 ppm irritation threshold for humans; at 2 ppm effects were severe
AEGL-3	9.6 ppm 3.0 mg/m^3	4.8 ppm 15 mg/m^3	2.6 ppm 8.1 mg/m^3	1.9 ppm 5.9 mg/m^3	NOEL for lethality

Nitric oxide, CAS No. 10102-43-9

Chemical Manager: Dr. Loren Keller, Oregon State University
Author: Dr. Carol Forsyth, ORNL

Loren Koller explained that the development of AEGLs for nitric oxide is currently on hold awaiting new data that were presented at the 1998 Society of Toxicology Annual Meeting and that would be useful in developing AEGL-2 and AEGL-3 values (Attachment 14). The new data have not yet been transferred for use by the NAC/AEGL but should be available by the September meeting. The half-life of NO in atmospheric and kinetics were briefly discussed by Kyle Blackman (Attachment 15). The issue of conversion of NO to NO_2 is also being addressed as are the mechanisms of toxicity of these two compounds and their possible sources. Following a brief discussion, the following recommendations were made: (1) derive AEGL values for NO and NO_2, (2) add the executive summary for NO_2 as an appendix to the NO technical support document (TSD), and (3) note in the NO TSD, that NO_2 is of concern but exact exposure concentrations will be impossible to predict. If substantial changes are required in the TSDs, revised documents will be distributed in July pending availability of the new data.

Crotonaldehyde mixture CAS No. 4170-30-3 & *trans* isomer CAS No. 123-73-9

Chemical Manager: Dr. Doan Hansen, Brookhaven National Laboratory
Author: Dr. Sylvia Milanez, ORNL

Sylvia Milanez presented a summary of data available for crotonaldehyde and the derivation of the draft AEGLs (Attachment 16). Bob Benson motioned (second by Richard Niemeier) to accept the AEGL-1 values as proposed in the TSD (0.19 ppm for all time points, based upon irritation threshold). The motion carried unanimously [YES: 23, NO: 0, ABSTAIN: 0]. The draft AEGL-2 values proposed in the TSD were based upon the lowest exposure (expressed in the key study as a concentration x time product) resulting in pulmonary lesions in rats. (i.e., 8,000 ppm min). Although alternate AEGL values were proposed, the use of the Ct of 8,000 ppm-min as the threshold for bronchiolar lesions was accepted [YES: 19, NO: 2, ABSTAIN: 0] for determining the AEGL-2 values (motion made by Doan Hansen,second by Thomas Hornshaw). James A. Dego from Eastman Chemical Company indicated that use of the RD_{50} was not appropriate as an endpoint for AEGL-2. Following a brief discussion, Ernest Falke motioned (seconded by David Belluck) to accept the AEGL-3 values based upon time-specific data for the 30-min, 1- and 4-hr values, and that the 8-hr values be scaled from the 4-hr value (n = 1.2). The motion carried (YES: 20, NO: 1, ABSTAIN: 0] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CROTONALDEHYDE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	Irritation threshold
AEGL-2	8.9 ppm 2.5 mg/m^3	4.4 ppm 13 mg/m^3	1.1 ppm 3.2 mg/m^3	0.56 ppm 1.6 mg/m^3	Threshold for bronchiolar lesions, n=1 due to use of Ct (8000 ppm-min) rather than series of conc.-time values
AEGL-3	27 ppm 77 mg/m^3	14 ppm 40 mg/m^3	2.6 ppm 7.5 mg/m^3	1.5 ppm 4.2 mg/m^3	Lethality threshold in rats

Nickel carbonyl, CAS No. 13463-39-3

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Robert Young, ORNL

Although AEGL-1 values were deemed inappropriate and draft proposed AEGL-3 values for nickel carbonyl were approved by the NAC/AEGL at the December 1997 meeting (Meeting 8), time did not allow for addressing the data sets relevant to AEGL-2 values. Kyle Blackman opened the deliberations on nickel carbonyl by addressing salient issues regarding the degradation of the chemical in ambient conditions (Attachment 17). Robert Young provided an overview of the previous deliberations as well as data and issues concerning development of AEGL-2 values (Attachment 18). Sally Williams (INCO, Wales, UK) presented information (Attachment 19) on the use and properties of nickel carbonyl, stressing that it occurs only under strictly controlled conditions and that its use is restricted to only a few sites in the world aside from very small amounts occasionally produced in research laboratories. Additionally, she emphasized that monitoring of ambient nickel carbonyl levels is not currently feasible, and that development of AEGL values beyond 1 hr would be inappropriate due to the rapid degradation of the chemical. Following discussion of the developmental toxicity data, AEGL-2 values were approved [YES: 21, NO: 6, ABSTAIN: 2]; motion made by George Alexeeff, second by William Bress. It was also the consensus of the NAC/AEGL that 8-hr values for both AEGL-2 and AEGL-3 were inappropriate due to the properties of the chemical (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR NICKEL CARBONYL					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**

AEGL-1	NA	NA	NA	NA	Not appropriate; toxicity below odor threshold
AEGL-2	0.059 ppm 0.41 mg/m^3	0.042 ppm 0.29 mg/m^3	0.021 ppm 0.14 mg/m^3	NA	Developmental toxicity in hamsters; gestational exposure
AEGL-3	0.32 pm 2.2 mg/m^3	0.22 popm 1.5 mg/m^3	0.11 ppm 0.76 mg/m^3	NA	Estimated lethality threshold (LC_{01} of 3.17 ppm) in mice, UF=30; *n*=2

Hydrogen sulfide, CAS No. 7783-06-4

Chemical Manager: Dr. Stephen Barbee, Olin Corporation
Author: Dr. Cheryl Bast, ORNL

The deliberations on hydrogen sulfide were deferred to the next meeting following issues/concerns expressed by several NAC members (George Alexeeff, Calif. EPA: David Belluck, MN Pollution Control Agency; Zarena Post, TX Nat. Resource Conserv. Comm.) regarding assessments by their respective states.

Chloroform, CAS No. 67-66-3

Chemical Manager: Dr. Stephen Barbee, Olin Corporation
Author: Dr. Robert Young, ORNL

Steve Barbee commented on the proposed draft AEGLs for chloroform and the assumptions used to derive them. Robert Young presented an overview of the draft values and the key data sets pertinent to each AEGL level (Attachment 20). Data consistent with AEGL-1 effects were unavailable. Limited data in humans indicated that no toxic effects were associated with exposures producing strong but not unpleasant odor. It was the consensus of the NAC/AEGL that AEGL-1 values for chloroform be considered inappropriate due to properties of the chemical [YES: 22, NO: 1, ABSTAIN: 0]. Motion by David Belluck (second by Richard Thomas) for the development of draft AEGL-2 values, the use of human data from older studies were originally used to estimate a narcosis threshold. However, following discussion of the available data and its relevance to the AEGL process, it was the consensus of the NAC/AEGL to use rodent developmental toxicity data as the basis for the AEGL-2. The total uncertainty factor was 3 for protection of sensitive populations. Due to greater sensitivity of rodents in metabolism and toxicity, no further adjustment by uncertainty factor application was warranted. A motion to accept the AEGL-2 values was made by Larry Gephart (second by Richard Thomas); the motion passed [YES: 20, NO: 3, ABSTAIN: 0]. The AEGL-3 values were based upon a lethality threshold estimated by a one-third reduction in a rat 4-hr LC50 (9780 ppm/3 = 3260 ppm). An uncertainty factor of 3 was applied

for protection of sensitive individuals. Based upon PB-PK modeling of metabolism/disposition of chloroform in rodents species, humans appear to be less sensitive to the toxic effects of chloroform. Data were unavailable for empirically deriving a scaling exponent (*n)* and, therefore, temporal extrapolation for all AEGL values utilized an default value for *n (n* = 2). The AEGL-3 values were accepted [YES: 22, NO: 1, ABSTAIN: 0] (motion by Steve Barbee, second by George Rodgers) (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR CHLOROFORM					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	NA	NA	NA	NA	Not appliable due to properties of chemical
AEGL-2	120 ppm 584 mg/m^3	88 ppm 429 mg/m^3	44 ppm 214 mg/m^3	31 ppm 151 mg/m^3	Based on NOAEL for developmental effects in rats following gestational exposure to 100 ppm; UF=3
AEGL-3	920 ppm 4480 mg/m^3	650 ppm 3166 mg/m^3	330 ppm 1607 mg/m^3	230 ppm 1120 mg/m^3	Lethality threshold estimatead by ⅓ reduction in rat 4-hr LC_{50}; UF=3

Carbon tetrachloride, CAS No. 56-23-5

Chemical Manager: Dr. William Bress, Vermont Dept. of Health
Author: Dr. Robert Young, ORNL

In response to concerns expressed by John Morawetz (ICWU), studies and issues pertaining to human lethality following acute exposure to carbon tetrachloride were discussed. Robert Young presented an overview of studies distributed to the NAC/AEGL by John Morawetz that focused on human lethality as well as studies addressing the issue of P-450 induction and its enhancement of carbon tetrachloride toxicity (Attachment 21) . Special focus was placed upon the Norwood et al. (1950) study as a possible driver for the AEGL-3 values because it identified an individual that would not have been protected by the current draft proposed AEGL-3 values accepted by the NAC/AEGL at the December 1997 meeting (Meeting 8). There was discussion regarding the reliability of the Norwood report and precision of the exposure data. There was also discussion on the effect of P-450 induction on lethality and nonlethal toxicity of carbon tetrachloride. Use of the Norwood et al. data as the primary driver for the AEGL-3 values would lower the AEGL-3 values somewhat (189 ppm, 143 ppm, 83 ppm, and 63 ppm for the 30 min, 1-, 4-, and 8-hr periods, respectively) relative to the draft proposed values of 230 ppm, 170 ppm, 99 ppm, and 75 ppm. It was decided that a poll of the NAC/AEGL would be taken at the next meeting to determine if the draft proposed AEGL-3 values should be retained or if they should be revised based upon the Norwood et al. report. The draft proposed AEGL values accepted at the December 1997 meeting are shown below.

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	16 ppm 100.6 mg/m^3	12 ppm 75.5 mg/m^3	6.9 ppm 43.4 mg/m^3	5.2 ppm 32.7 mg/m^3	Nervousness, slight nausea in human subjects

AEGL-2	90 ppm 566.1 mg/m^3	68 ppm 427.7 mg/m^3	39 ppm 245.3 mg/m^3	30 ppm 188.7 mg/m^3	Nausea, vomiting, headache in humans subjects (intolerable to one of four subjects)
AEGL-3	230 ppm 1,446.7 mg/m^3	170 ppm 1,069.3 mg/m^3	99 ppm 622.7 mg/m^3	75 ppm 471.8 mg/m^3	Estimated lethality threshold (LC_{01}=5,135.5 ppm in rats)

ADMINISTRATIVE ISSUES

Roger Garrett addressed issues regarding the time-line for document preparation, distribution, and review, and the overall responsibilities/function of the AEGL Development Team. He presented a potential schedule for preparation of draft TSDs (Attachment 22).

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

September 14-16, 1998, Oak Ridge, TN
December 7-9, 1998, Washington, DC
March 18-19, 1999, New Orleans, LA (after SOT)

These meeting highlights were prepared by Bob Young and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC Meeting No. 10 Agenda
2. NAC Meeting No. 10 Attendee List
3. Draft Guideline for Carcinogens - Richard Thomas
4. Information of potential applications of anesthetic effects for AEGLs development - George Rodgers
5. Correspondence on Bromine testing - Larry Gephart
6. Bench Mark Dose Approach discussion I - Bob Benson
7. Bench Mark Dose Approach discussion II - Bob Snyder
8. Influence of toxicity averaging time on cloud penetration for accidental releases - Ken Steinberg
9. Comments of draft AEGL of Propylene oxide from Chemical Manufacturers Association
10. CMA Propylene Oxide Panel - Larry Andrews
11. Human Exposure & Experience to Propylene Oxide - Susan Ripple
12. Data analysis of Acrolein - Cheryl Bast
13. Data analysis of Peracetic acid - Kowetha Davison
14. Data analysis of NO_2- Loren Koller and Carol Forsyth
15. Data analysis of NO_2 in atmospheric air - Kyle Blackman
16. Data analysis of Crotonaldehyde mixture - Sylvia Milanez
17. Kinetics of Nickel carbonyl - Kyle Blackman
18. Data analysis of Nickel carbonyl - Bob Young
19. Comments of draft AEGL of Nickel carbonyl - Sally Williams
20. Data analysis of Chloroform - Bob Young
21. Data analysis of carbon tetrachloride - Bob Young
22. Schedule for draft AEGL preparation - Roger Garrett

LIST OF APPENDICES

A. Approved NAC-9 Meeting Highlights
B. Ballot for Acrolein
C. Ballot for Peracetic acid
D. Ballot for Crotonaldehyde mixture
E. Ballot for Nickel carbonyl
F. Ballot for Chloroform

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

Old Post Office, M09
1100 Pennsylvania Avenue, N. W.
Washington, D.C. 20506

NAC-10

AGENDA

Monday, June 8, 1998

10:00 - 10:15 AM	Introductory remarks and approval of NAC/AEGL-9 highlights (George Rusch, Roger Garrett and Paul Tobin)
10:15 - 12:00	Status Reports: • Draft guideline for carcinogens (Richard Thomas) - 10 min. • Draft guideline for Anesthesia (George Rodgers) - 10 min. • Bromine testing (Larry Gephart) - 5 min. • Benchmark dose approach (Bob Benson/Bob Snyder) - 30 min. • Tests for sensory irritations (Pam Dalton) - 30 min. • Application of AEGLs to Air Release Dispersion Model (Ken Steinberg) - 20 min.
12:00 - 1:00 PM	**Lunch**
1:00 - 2:00	SOP status report (Ernie Falke)
2:00 - 3:00	Revisit Draft AEGLs: • Propylene oxide: industrial input for AEGL-1 (Jim Holler) - 45 min. • Carbon tetrachloride: issue of sensitive individuals for AEGL-3 (Bill Bress) - 15 min.
3:00 - 3:15	**Break**
3:15 - 5:15	Acrolein (Bob Snyder/Cheryl Bast)

Tuesday, June 9, 1998

8:30 - 10:00 AM	Peracetic acid (Mark McClanahan/Kowetha Davidson)
10:00 - 10:15	**Break**
10:15 - 12:15	Hydrogen sulfide (Steve Barbee/Cheryl Bast)
12:15 - 1:15 PM	**Lunch**
1:15 - 2:45	Nickel carbonyl (Kyle Blackman/Bob Young)
2:45 - 3:00	**Break**
3:00 - 5:00	Crotonaldehyde mixture & *trans*-isomer (Doan Hansen/Sylvia Milanez)

Wednesday, June 10, 1998

8:30 - 9:00 AM	Overview of Nitric oxides (Loren Koller/Carol Forsyth)
9:00 - 10:30	Chloroform (Steve Barbee/Bob Young)
10:30 - 10:45	**Break**
10:45 - 11:15	Chloroform (continued)
11:15 - 11:45	NAS status report
11:45 - 12:30 PM	Administrative issues • Revisit time line for TSDs
12:30	Adjournment

Attachment 2

ATTENDANCE SHEET

SUBJECT: M09- 1100 PENN AVE

DATE:
TIME:

LOCATION: ~~Ariel Rios - Green Room~~

Name	Signature	Organization	Phone Number
Zarena Post	Zarena Post	TNRCC	512 239 1332
Robert Benson	Robert Benson	EPA Region 8	303-312-7070
PATRICIA IALCOTT		U IDAHO	208.885.7081
Loren Keller	Loren D Keller	Oregon State University	541 737 5547
DAVE Bellum	D. A. Bellum	MPCA	612-296-7874
George Alexeeff	George Alexeeff	Cal/EPA	510-540-2907
Richard Thomas	Richard Thomas	ICF-A	703 [illegible] 134-1454
ROGER GARRETT		EPA	202-260-4302
George M Fusch	George Fusch	Allied Signal	973-455-3672
Paul Tobin	Paul Tobin	EPA	202 260-1736
LJZ Claudio		Mount Sinai	212 241 6173
JOHN R. BURKE FOR DR. FRANK VINCENT	John R. Burke	Fort James Corp	202-789-6007
Amy Burk	Amy Burk	International Life Sciences Institute	202-659-3306

Name	Signature	Organization	Phone Number
BARRY HOOBERMAN		ENVIRON CORP	703-516-2332
LARRY ANDREWS	L. F. Andrews	ARCO Chem.	610-359-4876
Ken Steinberg	KW Steinberg	Exxon Research & Eng. Co	(973) 765 1209
James Deyo		Eastman Chem.	423-229-5208
Susan Ripple	Susan Ripple	Dow Chemical	517 636 5572
Lyse Helsing	Lyse Helsing	Chemical Board	202/261-7607
Steven BAYARD		OSHA	202-219-7105 x130
[illegible] KING		EOP/OMP	202 395-7318

→ OVER

ATTENDANCE SHEET

SUBJECT:

DATE: June 8, 1998

TIME:

M09- 1100 PENN AVE

LOCATION: ~~Ariel Rios - Green Room~~

Name	Signature	Organization	Phone Number
Ernest V. Falke	Ernest V. Falke	US EPA	202 260-3433
GEORGE CUSHMAC	George Cushmac	USDOT/RSPA	202-366-4493
Bob Snyder		Nutec Inv	908-441-3[illegible]
DOAN HANSEN	Doan Hansen	DOE/BNL	516 344-7535
JONATHAN BOWAK		ACOEM	203-777-6611
TOM HORNSHAW	Thomas C. Hornshaw	IL EPA	217-785-0830
Larry Gephart	Larry Gephart	Exxon Biomedical	732 873-6319
MICHELLE SCHAPER	Michelle Schaper	MSHA/EVEST	(703) 235-1570
Benjamin A. Jackson	Benjamin A. Jackson	CONSULTANT	(301)-871-6820
RICHARD W. NIEMEIER	Richard W. Niemeier	NIOSH	(513) 533-8388
William C. Bress	William C. Bress	ASTHO/VERMONT	802-863-7598
WILLIAM PAPKO	William Papko	USEPA NCEA	202-564-3309
MARK A. MCCLANAHAN	Mark A. McClanahan	CDC/NCEH	770-448-7297
JIM HOLLER	Jim Holler	ATSDR	404-639-6308
ROBERT YOUNG	Robert Young	ORNL	(423) 574-4573
Cheryl Bast	Cheryl Bast	ORNL	423-574-7581
Deirdre Murphy	Deirdre L. Murphy	EPA/OAR/OAQPS	919-541-0729
Pamela Dalton	Pamela Dalton	Monell Chem Senses Ctr	215-898-5595
Po-Tzung Lin	Po-Tzung Lin	ORNL	423-574-7803
Kenneth R. Stitt II		US NAVY	937-255-6058
GLENN LEACH	Glenn Leach	U.S. ARMY - CHAPPM	410-671-2176
John Morawetz	John S. Morawetz	ICF Inc/UFAW	513-621-8557
Thomas Sobotka	Thomas Sobotka	FDA	301 594-5881
Steven J. Barbee	Steven J. Barbee	Olin Corp/NIHA	203-495-8550 x5435
George Rodgers	George Rodgers	AAPCC	502-852-8626

→ OVER

Guideline for Carcinogens

(June 1998)

The evaluation of the carcinogenicity of a chemical resulting from acute exposures in humans should be based on analysis of all relevant data, both positive and negative response data. The AEGL Committee will follow a weight-of-evidence approach to this evaluation consistent with the biological variability observed in experimental studies. Laboratory animal studies may show variable results depending on the substance to be tested, species used, route of exposure, dose, and other factors. Further, some studies may be more important than others in ascertaining the biologic response in humans from chemical exposure. Greater importance is attached to those studies that more relevant to estimating effects in humans as determined by review on a case-by-case basis. The weight-of-evidence approach to evaluating carcinogenic hazard to humans serves as the basis for most carcinogen classification systems and will be used by the AEGL Committee in decisions on the carcinogenicity chemicals under review.

Scientists and regulators have generally found that extrapolation from species to species is justifiable and that chemicals that have produced biologic responses in laboratory animals will also do so in humans. Data for assessing the strength of conclusions to be drawn from laboratory animal studies should include information on comparative metabolic pathways, pharmacokinetics, routes of exposure, mechanisms of action, and organ or species differences in response. When pharmacokinetic models for calculating deliver dose and cross-species extrapolation have been developed, pharmacokinetic information should be incorporated into the quantitative risk estimates.

Human epidemiologic and other types of investigation such as clinical studies and accidental exposure reports should be used to ascertain the carcinogenic potential of the

substance under consideration. Human epidemiological studies are often difficult to evaluate, because of uncontrolled variables, however they present important primary data in the Committee's evaluation.

In the absence of quantifiable human exposure data, it is usually assumed that long-term bioassay data from animal studies will be used directly to derive acute exposure risk estimates in humans. Cancer potencies are generally based on dose-response relationships generated from laboratory animal bioassays. These bioassays are conducted in rodents exposed to doses that are several orders of magnitude greater than those for which risks are to be estimated. The selection of data for estimating risk is usually from the most sensitive strain or species of animal tested in order to produce conservative estimates.

Quantitative cancer risk estimates can be expressed as either potency or unit cancer risk. The EPA estimates of cancer potency (q*), defined as the upper-bound on the slope of the linear portion of a dose-response curve at low doses, will be used by the Committee to develop its estimates of cancer risks resulting from acute human exposure. The unit cancer risk is based on potency and is an upper-bound estimate of the probability of cancer development due to continuous lifetime exposure to one unit of carcinogen (e.g., 1 μg of chemical per cubic meter of air over a 70-year lifetime).

The AEGL Committee recognizes that there is only limited evidence that short-term or single exposures to carcinogenic substances are capable causing cancer in humans. In recognition that theoretically even limited exposure to chemical carcinogens could increase the risk of cancer, the Committee will conduct a separate quantitative risk assessment following the approach adapted by COT (NRC, 1993) for each chemical agent that is potentially carcinogenic in humans.

Forget the "laws"

Think!

Blood

Olive oil

1. Charle's law $\frac{T_1}{T_2} = \frac{V}{V_1} \times P$

2. Boyle's law $P \times V = K$

3. Gay-Lussac's law $\frac{T}{T_0} = \frac{P}{P_0}$ —

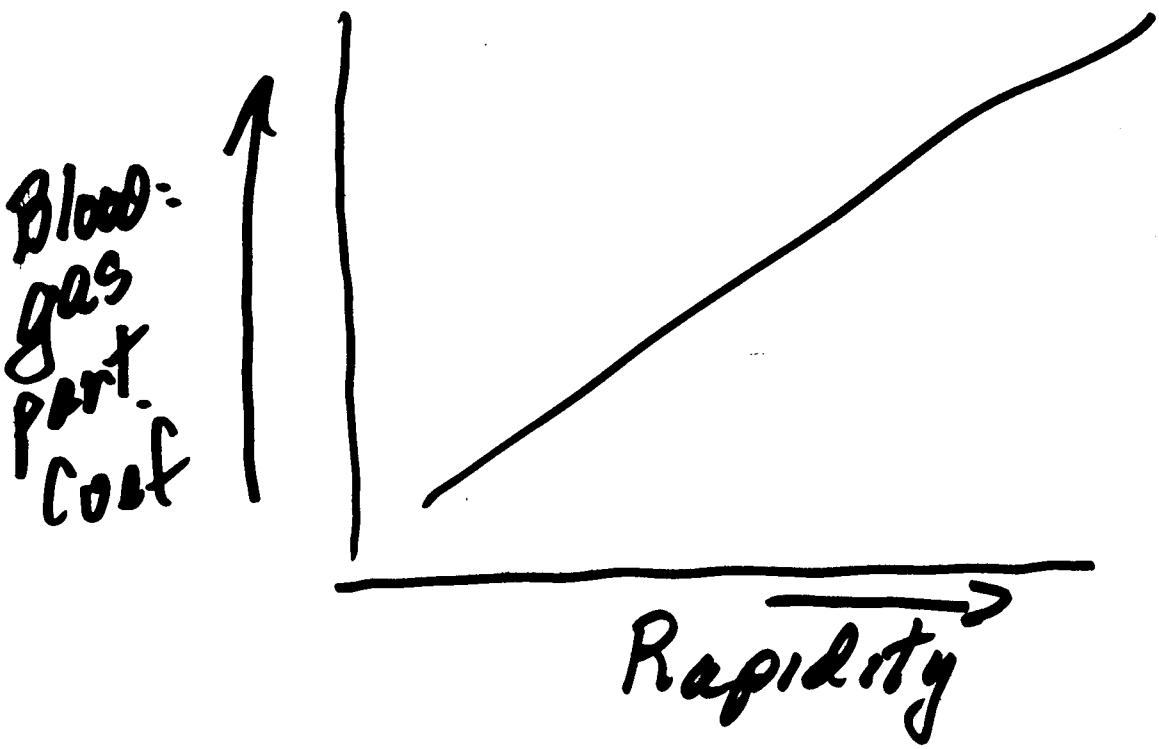
4. Dalton's law $P = P_1 + P_2 + P_3 \ldots P_n$

5. Henry's law
P (above soln) $\propto$ C (in solution)
Bunsen Sol. coef (α)
Ostwald " " (λ)

6. Avogadro's law - equal gas vols at same conditions contain same # molecules

7. LaPlaces Law (vap. pres in sphere)
$P = \frac{2 \times T}{r}$

Rapidity of onset of anesthetic effect.



Anesthetic Potency

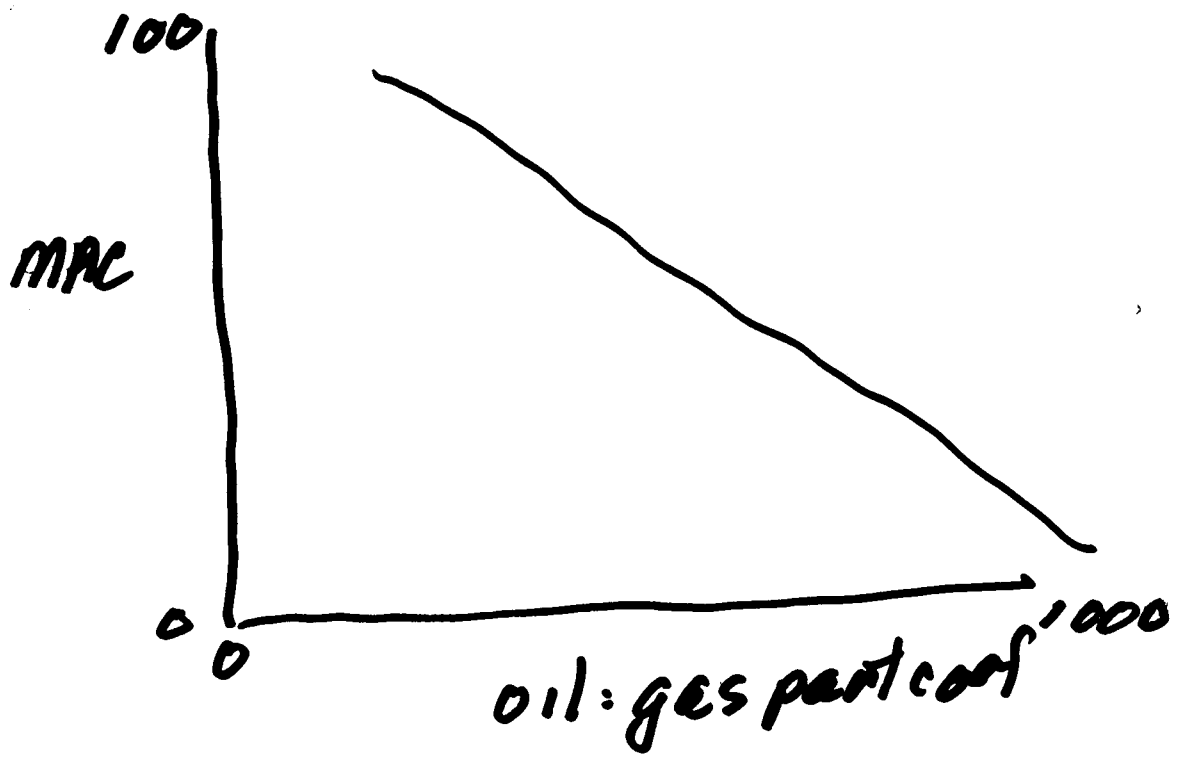
Units = MAC =
minimum alveolar concentration

MAC = conc. which prevents
movement in 50% of patients
in response to surgical
incision

RANGE for MAC 0.1 – 100+ mm

Individual variability ≈ 4X

MAC ∝ 1/oil:gas part. coef.



Children

Clinically more sensitive

(? reason)

? Magnitude

Variables in adults

To

Hct

Lung path.

Age

EXXON BIOMEDICAL SCIENCES, INC.

METTLERS ROAD, CN 2350, EAST MILLSTONE, N.J. 08875-2350

Toxicology Division
RICHARD D. PHILLIPS, Ph.D.
Director

April 2, 1998

Bromine AEGL

98MR 295

Dr. John Biesemeier
Great Lakes Chemical Corporation
Corporate Regulatory Affairs
1801 U.S. Highway 52 Northwest
West Lafayette, Indiana 47906-5310

Dear John:

This letter is a follow-up to our conversation on the need for additional toxicology data to support the development of Acute Exposure Guideline Levels (AEGLs) for bromine. As we discussed, the National Advisory Committee (NAC) developing AEGLs reviewed the available information on bromine at their last Committee meeting in March, 1998. This information considered is summarized in the draft Technical Support Document, which I have had forwarded to you. The NAC was unable to ascertain AEGLs with the existing data. The information viewed most useful for reducing the uncertainty in setting the values is listed below:

1) A comparative respiratory irritancy study (i.e., an Alarie study) in mice exposed to bromine and chlorine. This would provide a link to the available human chamber studies on chlorine, permitting more accurate assessment of AEGL 2 and AEGL 1 values.

2) 1- and 4- hour LC50 studies in rats. These data are needed to confirm the results of Birton and Anderson (1978), which indicate that bromine is somewhat less acutely toxic than chlorine. This would allow more accurate assessment of AEGL 3 values.

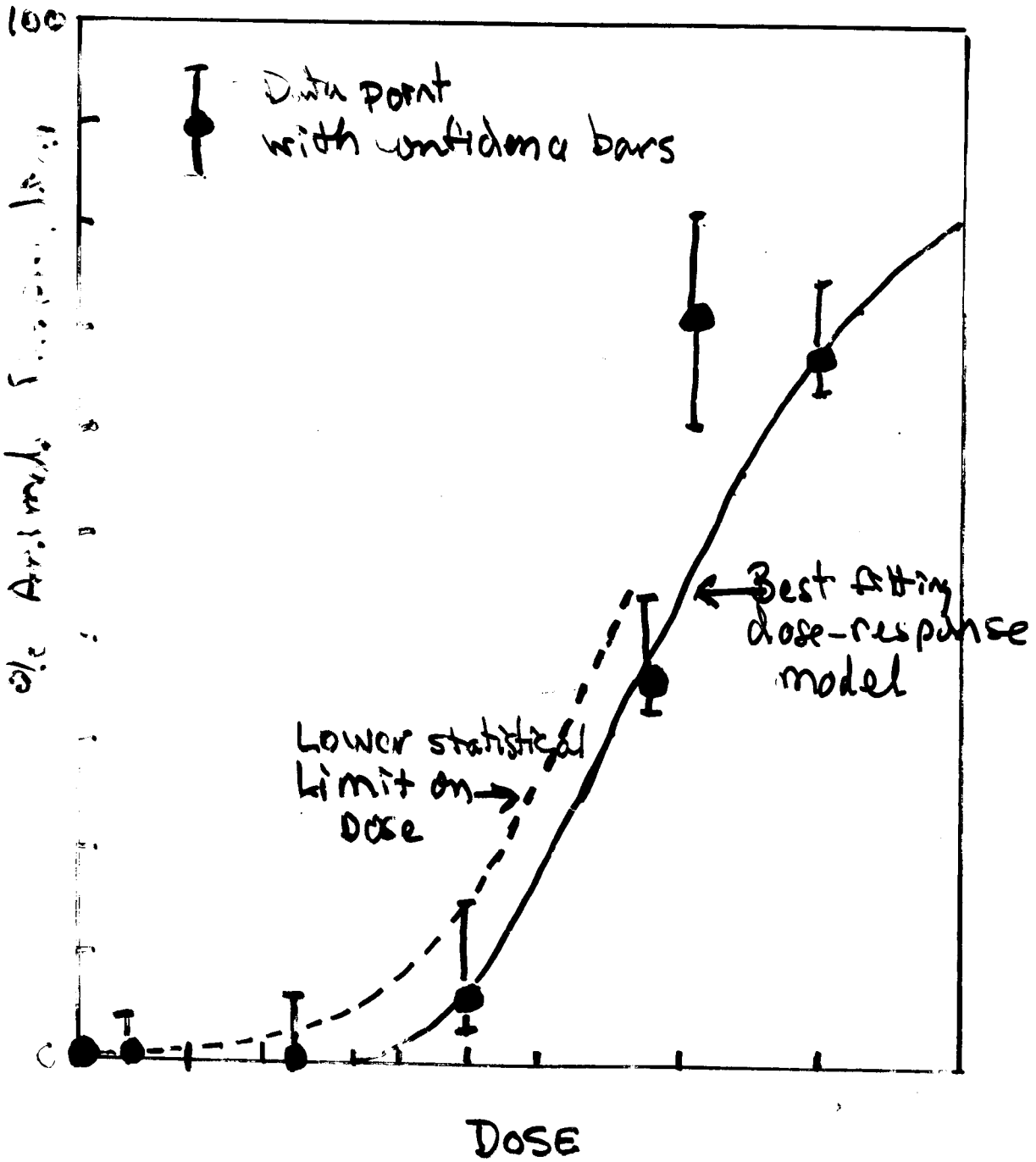
John, I appreciate your offer to present this issue to the appropriate trade and manufacturing groups. Please contact me if there are any questions on this request.

Very truly yours,

Larry A. Gephart

LAG:fvk

cc: R. Garrett, Environmental Protection Agency
D. Hansen, Brookhaven National Laboratory
Z. Post, Texas Natural Resource Conservation Commission
G. Rush, Allied Signal, Inc.
S. Talmage, Oak Ridge National Laboratory
P. S. Tobin, Environmental Protection Agency


100
Data point
with confidence bars
Best fitting
dose-response
model
Lower statistical
limit on
dose
DOSE

Quantal Polynomial Regression

$$P(d) = Q_0 + (1 - Q_0)\left\{1 - \exp[-Q_1 d - Q_2 d^2 - Q_3 d^3 - \ldots Q_K d^K]\right\}$$

$F(d)$ limits $0 \rightarrow 1$

Extra Risk

$$P(d) = \frac{[P(d) - P(0)]}{1 - P(0)}$$

User selects Degree of polynomial $1 \rightarrow$ [Dose grouper -1]

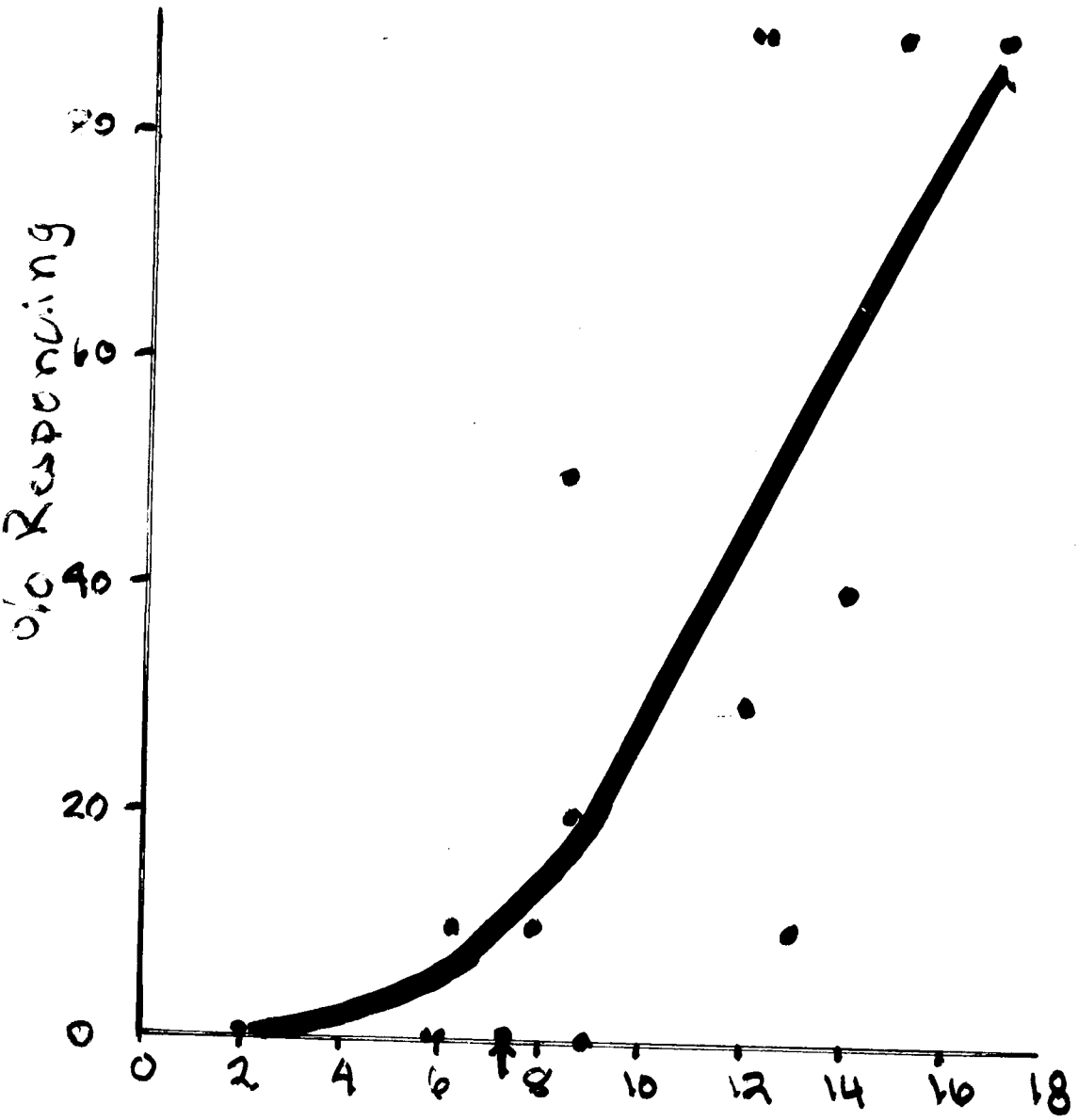
Program provides:

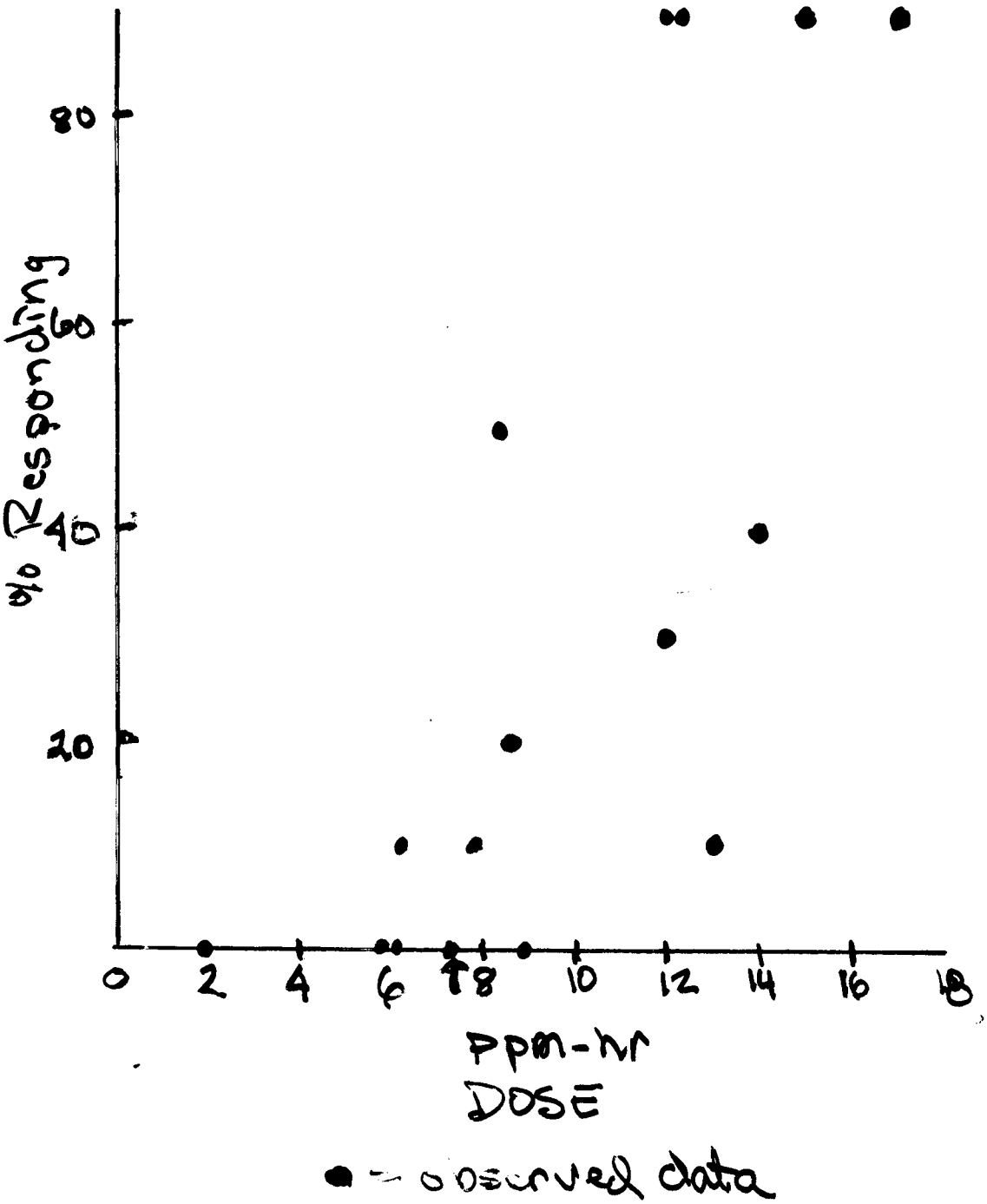
Predicted Response at dose

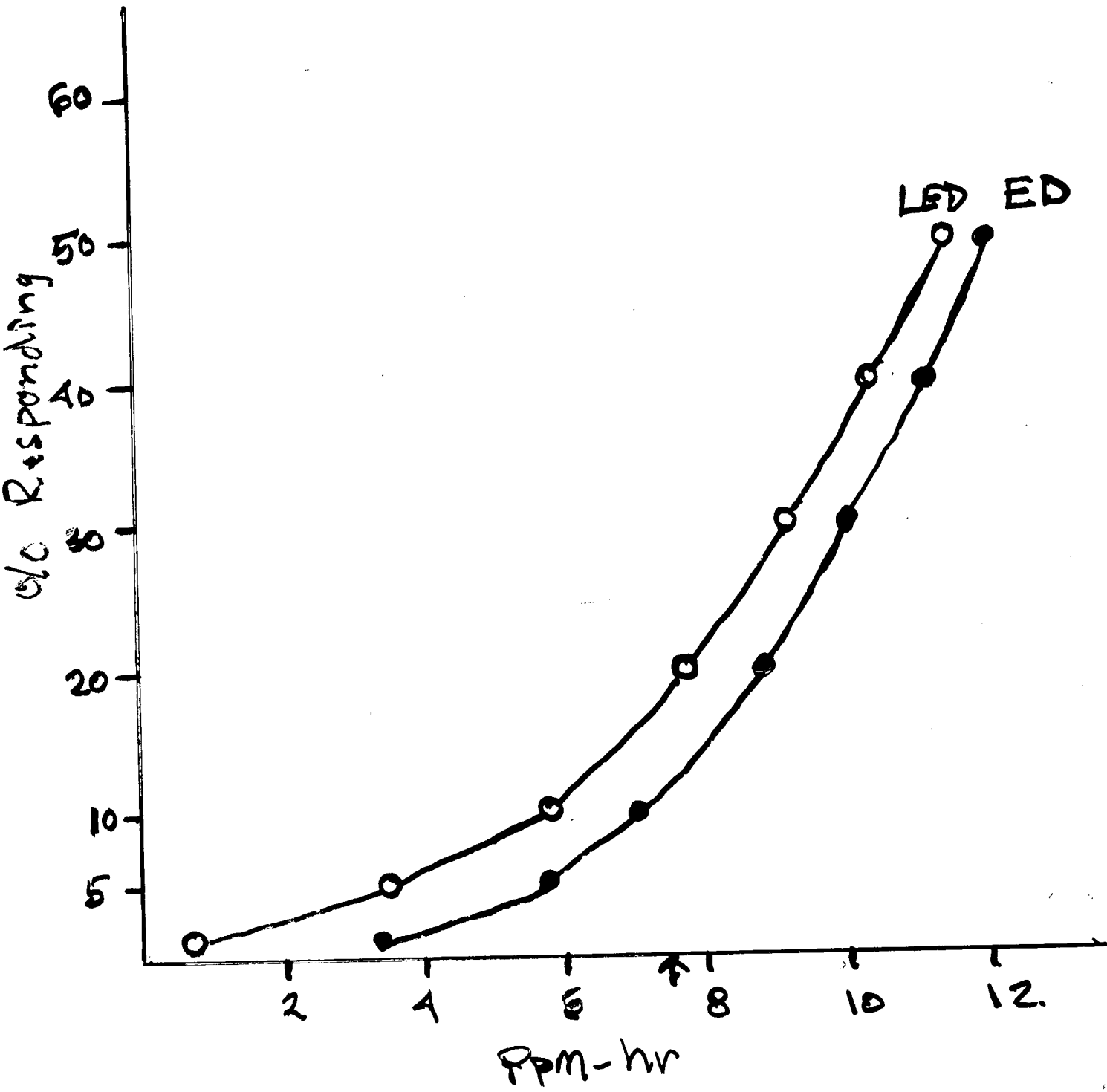
Estimates of $Q_0 \rightarrow Q_K$ (Best fit and Lower Limit)

Dose at a selected risk Level

Lower limit on dose at a selected risk level


% Response
0
20
40
60
80
0
2
4
6
8
10
12
14
16
18
Dose
rpm-hr
• observed data
– predicted


% Responding
80
60
40
20
0
2
4
6
8
10
12
14
16
18
ppm-hr
DOSE
● = observed data


60
50
40
30
20
10
5
% Responding
LED
ED
2
4
6
8
10
12.
Ppm-hr

ED_x ppm-hr

X %	10 min	30 min	60 min	All
50	14	9.9	11	12
10	10	6.2	5.9	7.1
5	9.1	5.1	4.6	5.8
1	6.9	3.4	2.7	3.5

LED_x ppm-hr

X %	10 min	30 min	60 min	All
50	13	8.9	4.5	11
10	8.1	5.1	4.1	5.8
5	4.8	3.5	2.4	3.5
1	1.0	0.83	0.51	0.72

onsequence of Drug-Receptor Interactions

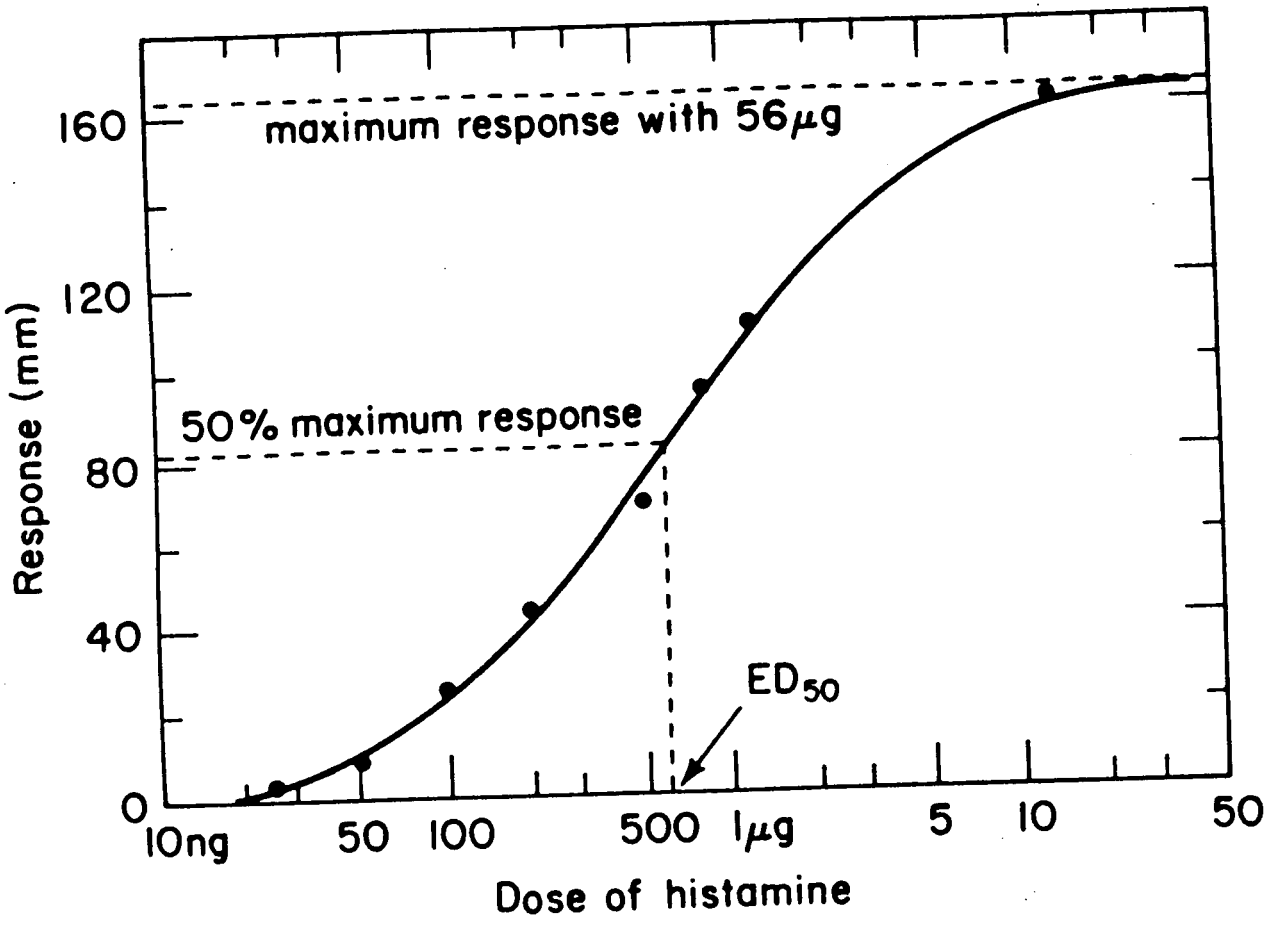
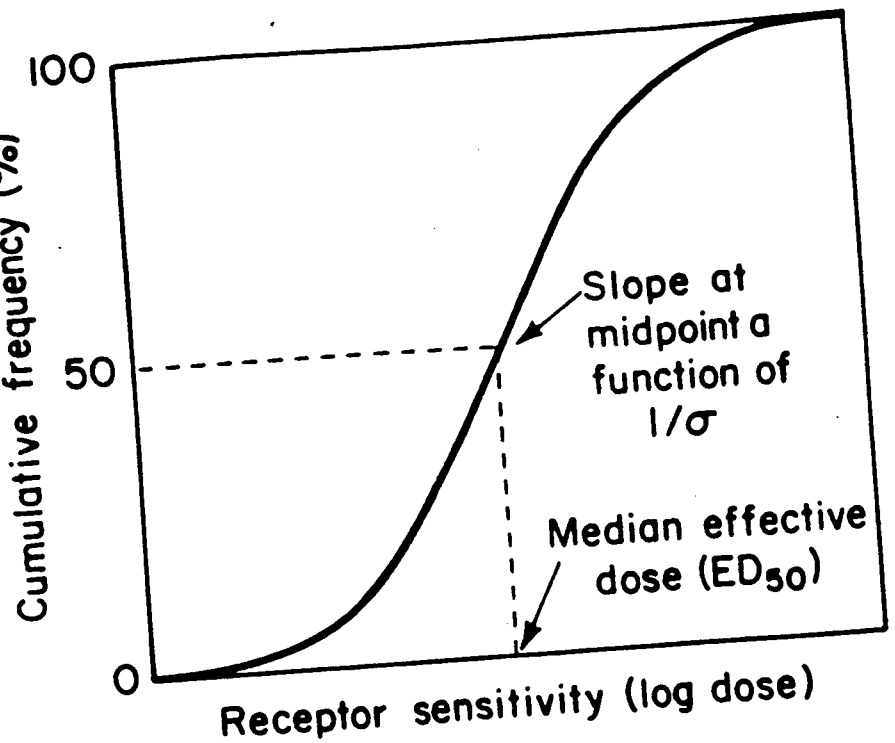


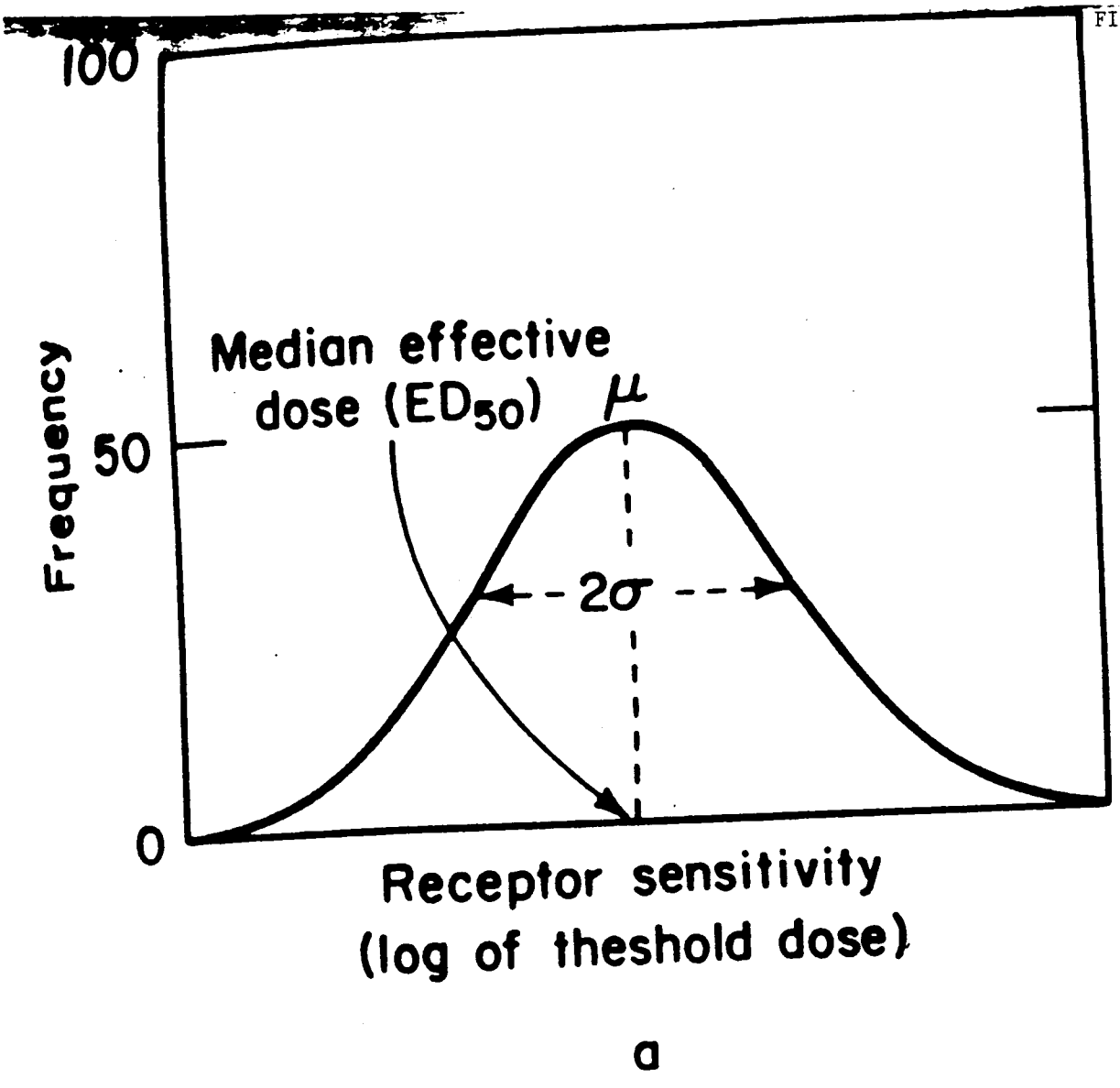
FIG. 1-57. LDR CURVE FOR HISTAMINE ACTING ON GUINEA PIG ILEUM IN A TISSUE BATH. *Response magnitude (read directly from a kymograph tracing) is proportional to actual contraction of the ileum. Histamine dose added to constant-volume tissue bath is shown on a logarithmic scale. (Adapted from*

FIGURE 2



b

Cumulative frequency distribution of (a). *The transformation results in a symmetrical sigmoid reminiscent of a typical LDR curve, whose slope is inversely proportional to the heterogeneity of postulated receptor sensitivities. (The symbol* ED_{50}, *as shown here, is an alternative way of writing ED50.)*



a

Log-normal distribution of sensitivities of individual receptors. The median effective dose is identical to the mean μ, and the breadth of the curve between the points of inflection is equal to twice the standard deviation.

FIGURE 4

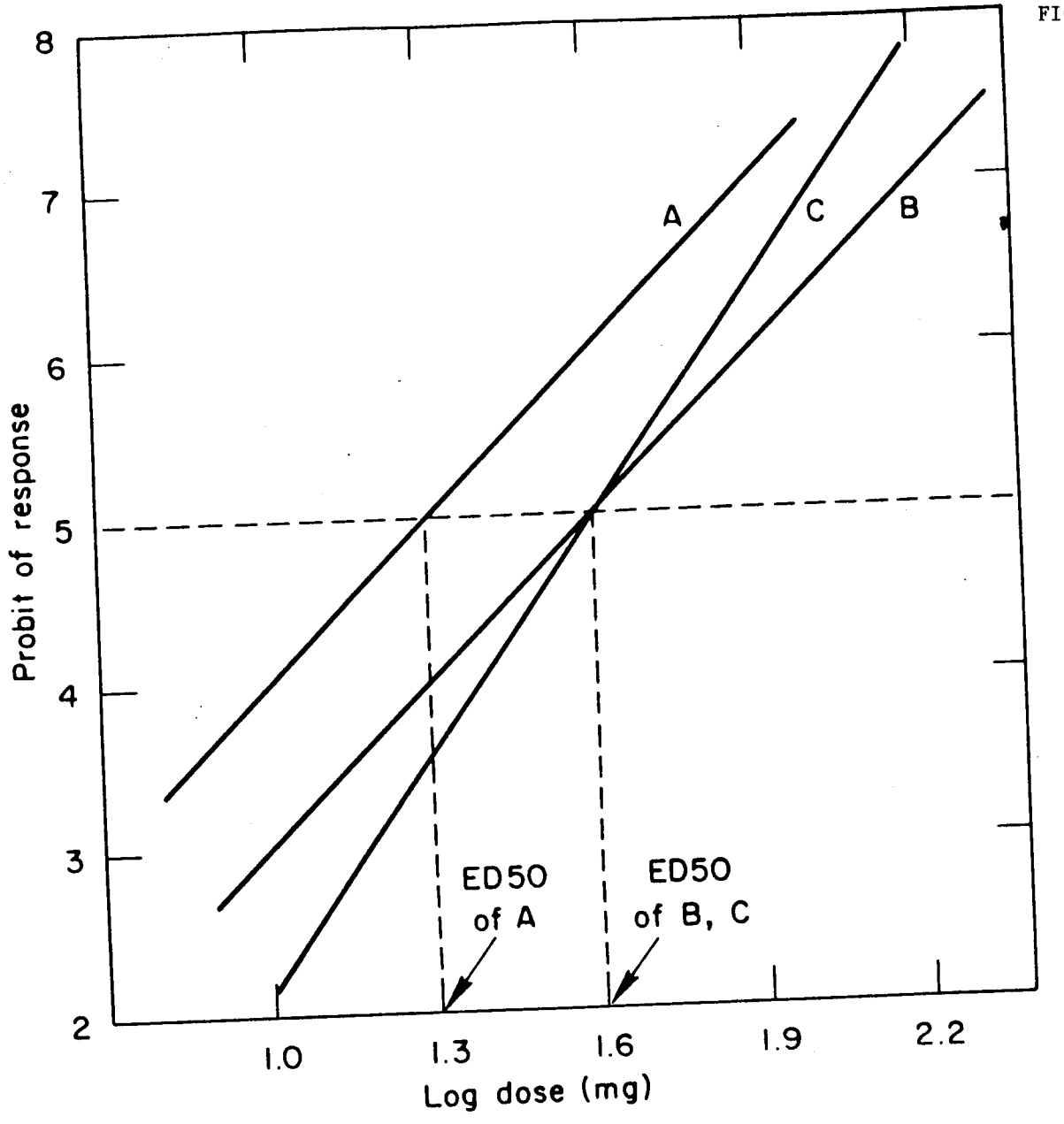
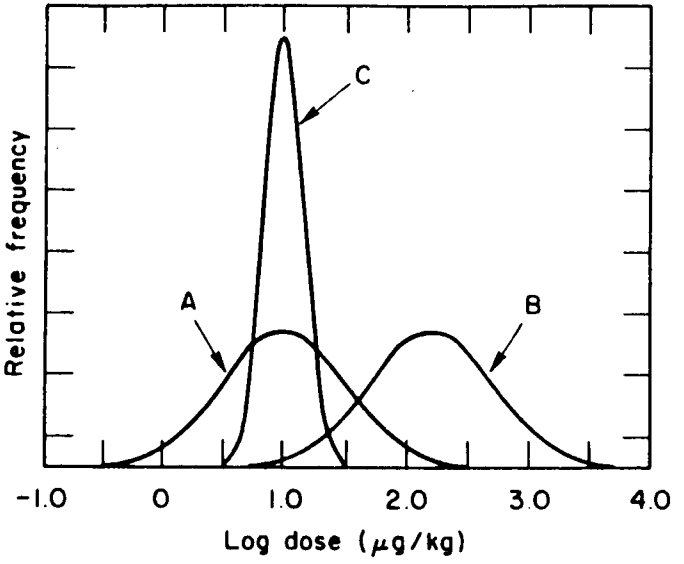
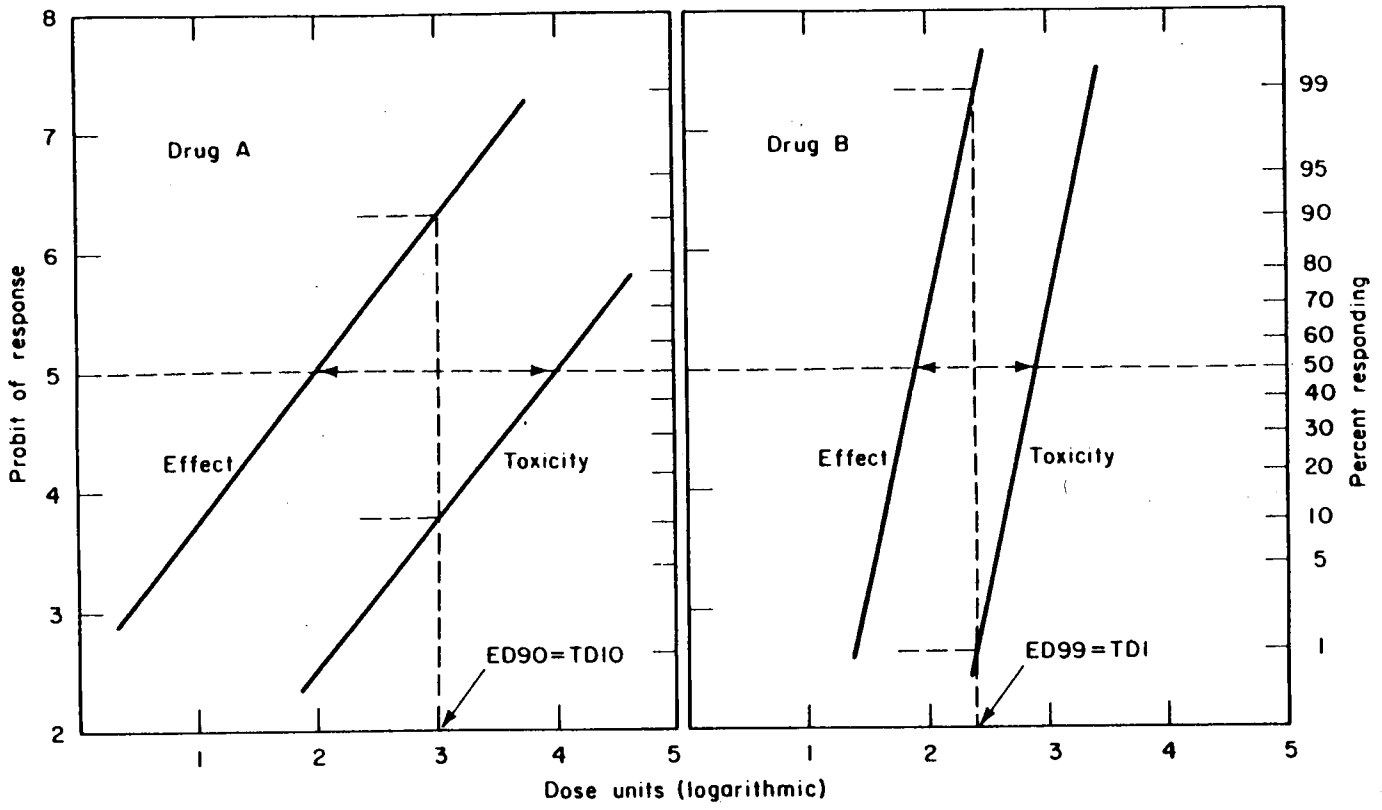


FIG. 5-5. LOG DOSE-PROBIT CURVES FOR THREE HYPOTHETICAL DRUGS.

FIG. 5-3. THEORETICAL DISTRIBUTIONS OF SENSITIVITIES TO THE LETHAL EFFECTS OF DRUGS IN A POPULATION. *The mean (and median) sensitivity to drug A is 1.0 log unit, i.e., 10μg/kg, and the standard deviation is ±0.5 log units. The mean sensitivity to drug B is 2.2 log units, i.e., 160μg/kg, and the standard deviation is the same as for drug A. Drug C has the same median lethal dose as drug A, but the population is much more homogeneous with respect to the drug's lethal action; the standard deviation is only ±0.16 log units.*

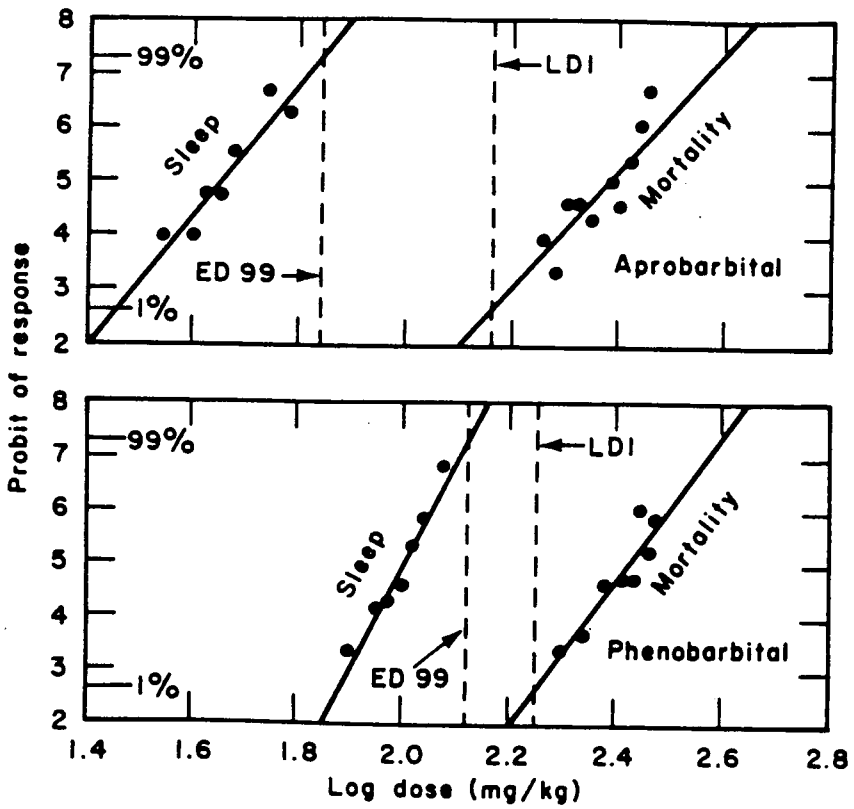




EFFECT OF SLOPE ON THE METHOD OF EXPRESSING THE THERAPEUTIC RATIO. *Log dose-probit curves for two hypothetical drugs, A and B, showing relationship between therapeutic effect and toxicity. These curves are steeper for drug* B *than for drug* A. *Scale of abscissas is in equal logarithmic increments of dosage. See text for analysis.*

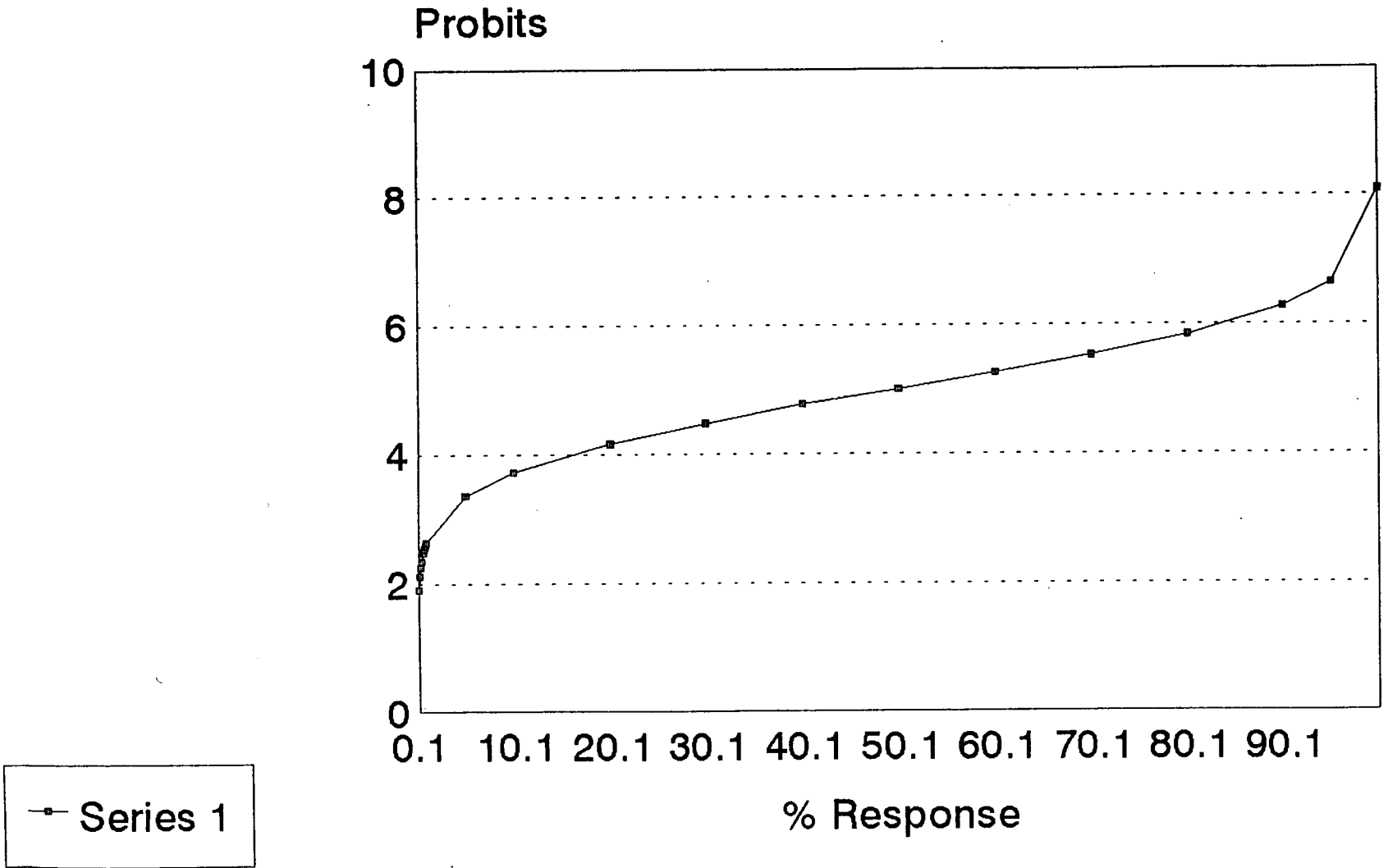
FIGURE 7

COMPARISON OF THERAPEUTIC RATIOS OF TWO BARBITURATES IN MICE. *Groups of 20 mice were injected with each dose subcutaneously. Sleep was defined as loss of righting reflex. Deaths were recorded at 24 hours. The log dose-probit lines are calculated, using appropriate weighting factors for the points at various probit values. (Adapted from Foster, Figs. 1 and 2.*[32])

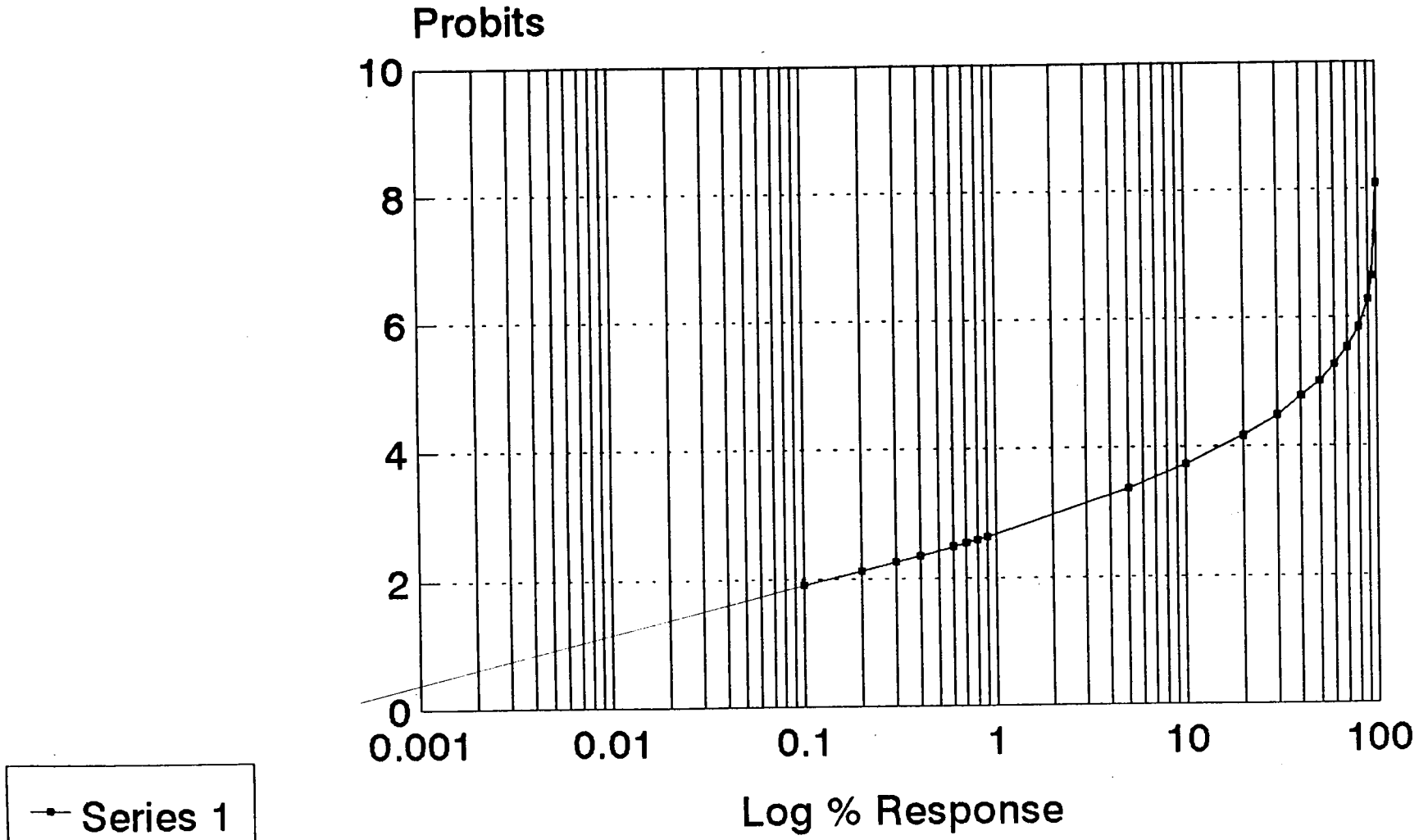


[32] R. H. K. FOSTER: Standardization of safety margin. *J. Pharmacol. Exper. Therap.* 65:1 (1939).

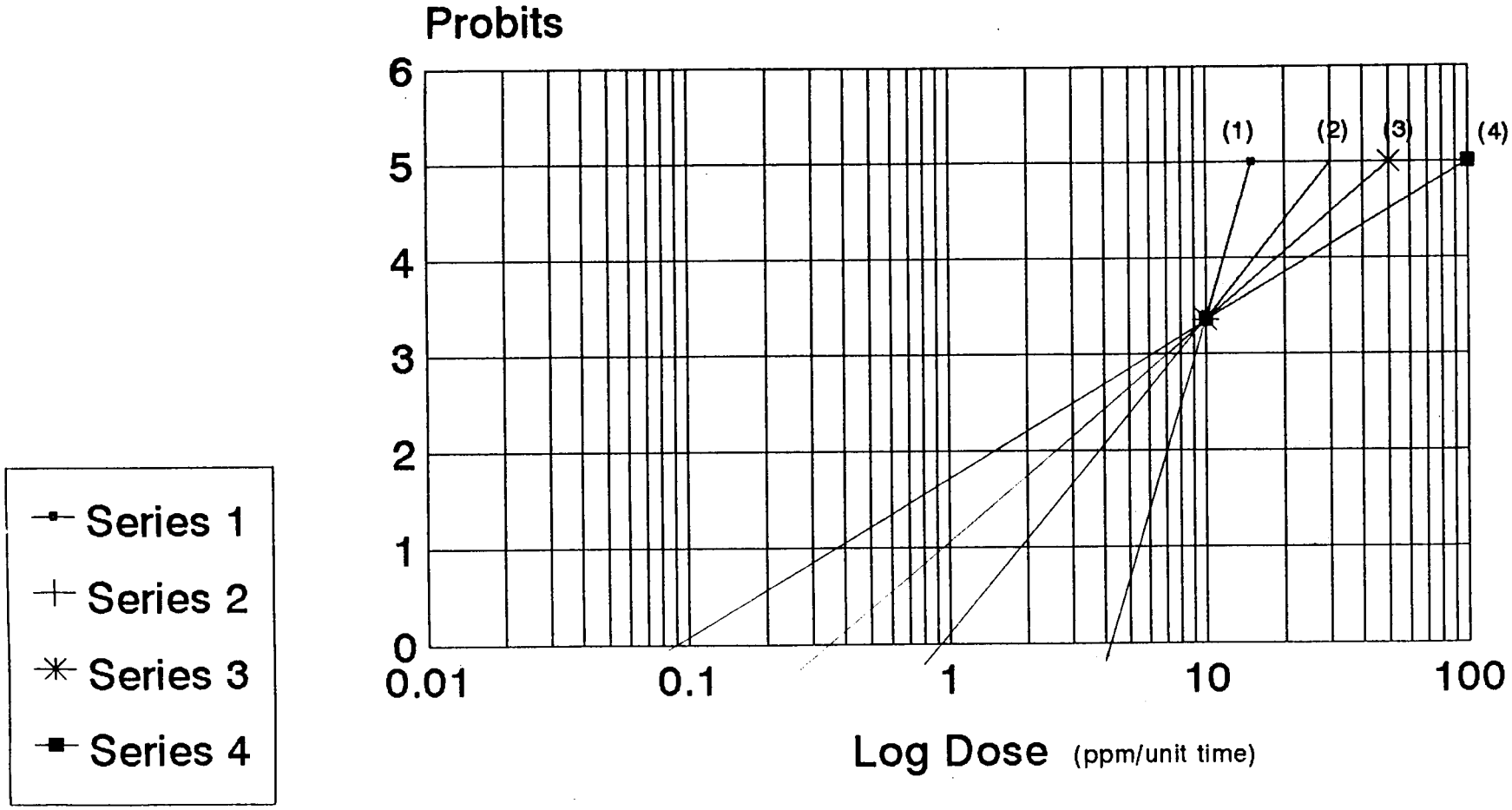
% Response v. Probits



Log % Response v. Probits



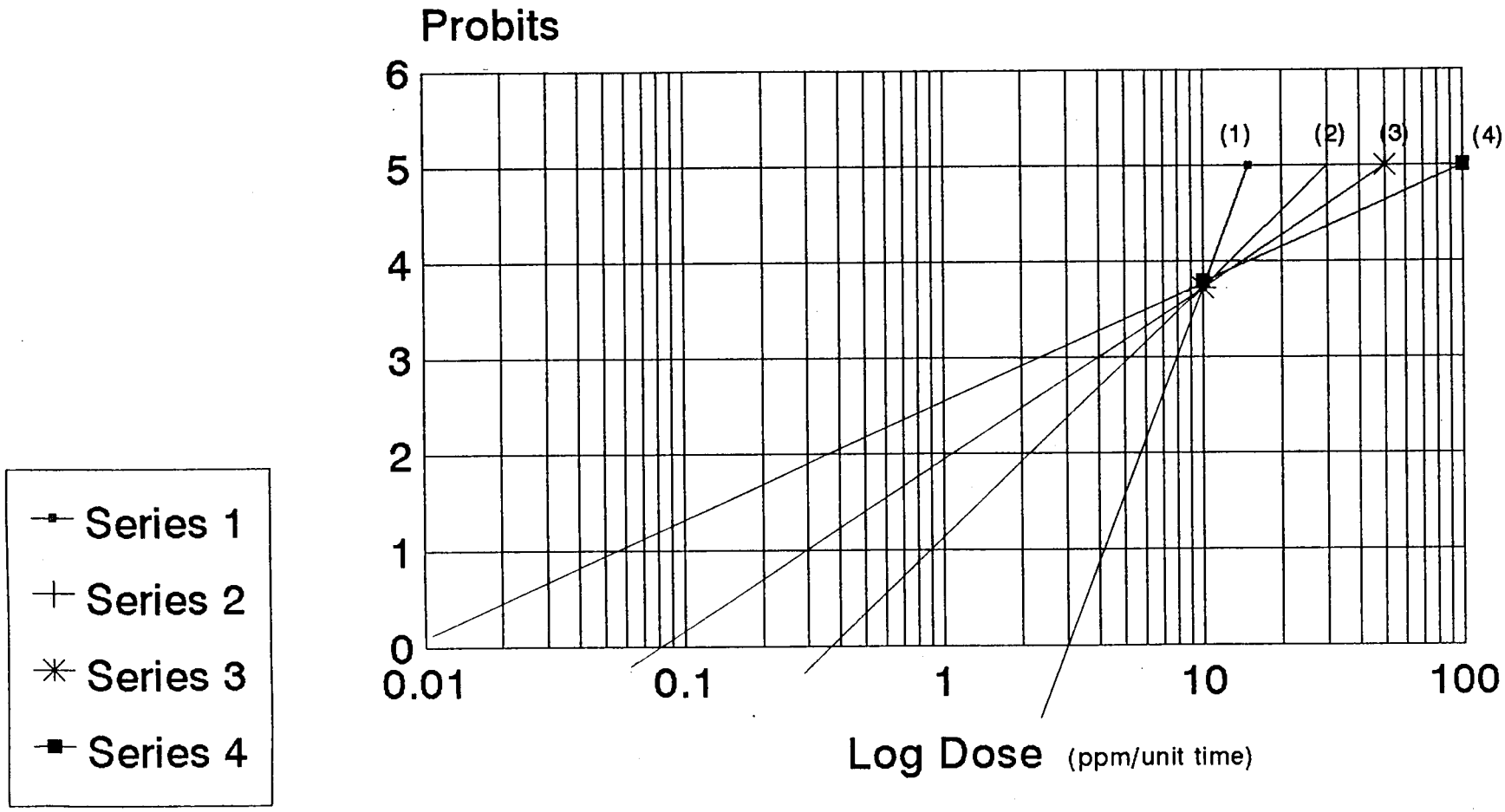
Log Dose v. Probits
4 chemicals with differing potency



probit 1 = 0.01% response
probit 0.5 = 0.001% response

FIGURE 11

Log Dose v. Probits
4 chemicals with differing potency



probit 1 = 0.01% response
probit 0.5 = 0.001% response

Influence of Toxicity Averaging Time on Cloud Penetration for Accidental Releases

June 8, 1998

AEGL National Advisory Committee Meeting

Washington, DC

Ken Steinberg

Exxon Research & Engineering Company

Attachment 8

Consequence Analysis For Accidental Releases

- Uses dispersion models
  - release description
  - meteorological conditions, and
  - appropriate AEGL health criterion consistent
- Provides results of toxic cloud footprint
  - a 'penetration' distance downwind and
  - a cross wind width

Worst-Case Cloud Penetration

- Analyze release scenario (e.g., short-duration accidents)
  - broad range of meteorological conditions
  - health concentration criteria (e.g. AEGL level-2 for various averaging-times)
- Greatest cloud penetration from modeling
  - Nighttime meteorology
    - » poorest conditions for dispersion
    - » longer cloud length and shallower depth

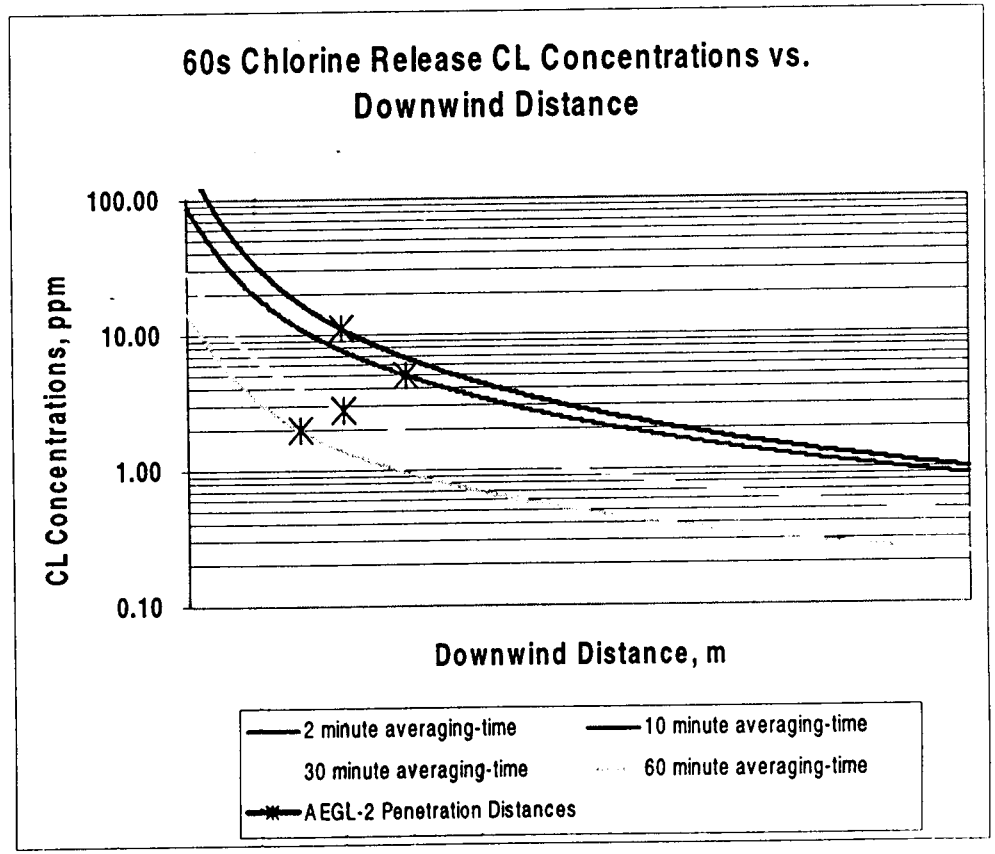
Worst-Case Cloud Penetration

(concluded)

- For short duration releases (SDRs), typically it's the shorter averaging-time AEGLs
  - SDR's disperse faster and travel shorter distances downwind
  - acute health effects from higher concentrations for short periods
- For long duration releases (LDRs), typically it's the longer averaging-time AEGLs
  - LDR's disperse more slowly causing longer-term, higher concentrations farther from the release point
  - acute health effects at lower concentrations for longer periods

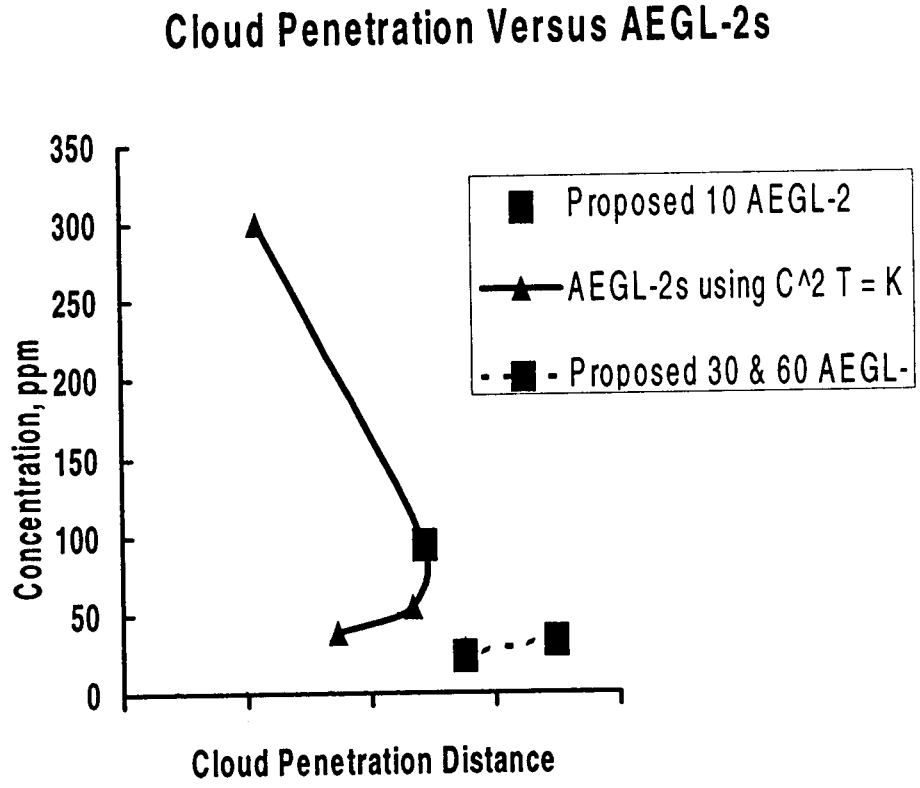
Example Cloud Penetration For A 60 second Release Of Chlorine

- Curves from dispersion modeling showing the predicted cloud centerline concentration as a function of downwind distance
  - 2, 10, 30, & 60 minute "AEGL-2" based on $C^2T = k$
- × marks penetrations to chlorine "AEGLs"
- Downwind cloud penetration distance greatest for 10 minute AEGL-2
- As expected, less for 2, 30 & 60 minute AEGL-2



Example Cloud Penetration For A 5 Minute Release Of HF

- Plotting only cloud penetrations for 10, 30, & 60 minute AEGL-2 & using "AEGL-2s" using C^2T = constant for 2, 10, 30, & 60 averaging-times
- Increasing penetration from 2 to 10 minute "AEGLs"...
- "AEGLs" using C^2T=constant show <u>expected</u> decreasing penetration for increasing 30-60 minute averaging-times
- Decrease in penetration for 30-60 minute AEGL-2s does not occur...



Results & Conclusion

- An apparent discontinuity exists in cloud penetration when using AEGL-2s for HF between the 10 and the 30/60 minute concentrations levels
- Dispersion results show a counter intuitive result that the greater cloud penetration for a short duration accidental release occurs for the 30/60 minute AEGL-2s than for the 10 minute AEGL (or 2 minute assuming C^2T=constant)
- If these AEGL-2s are correct, consequence analyses for even short duration events will need to considers a full range of averaging-times for the proposed HF AEGL-2s to determine worst-case cloud penetration distance

CHEMICAL MANUFACTURERS ASSOCIATION

Comments of the Propylene Oxide Panel
of the Chemical Manufacturers Association
on Acute Exposure Guideline Levels (AEGLs) for Propylene Oxide

---

Public Meeting -- June 8, 1998

I am Larry Andrews, Manager, Health Sciences and Regulatory Programs, of ARCO Chemical. I am appearing here today in my capacity as Chair of the Propylene Oxide Panel of the Chemical Manufacturers Association (CMA). The Panel has serious concerns with the second draft document and the AEGLs proposed for propylene oxide (PO).

The National Advisory Committee (NAC) AEGL committee was formed "to develop AEGLs through the combined efforts of stakeholder members from both the public and private sectors using a cost-effective approach that avoids duplication of efforts and provides uniform values while employing the most scientifically sound methods available.[1]" Unfortunately, the second draft AEGLs for PO do not reflect stakeholder input with respect to appropriate endpoints and safety factors. The AEGLs proposed for PO in the second draft are not justified by the scientific evidence and certainly not cost effective; they are unrealistic levels that are pegged to the ethylene oxide (EO) AEGLs although PO has an entirely different toxicology profile.

---

[1] 62 Fed. Reg. 58840 (Oct. 30, 1997).

AEGL values should be based both on human experience where available and on animal studies. The second draft does not use available human data because of a misconception that there is inadequate exposure information. Today we can fill that gap. We believe that once these data are considered, the NAC/AEGL will be able to develop more credible AEGLs for PO.

I. Human Data As Well as the Experimental Data Are Available and Should Be Used to Establish PO AEGL Values

The National Academy treatise on developing AEGLs states that human data as well as toxicology data should be used to develop AEGLs; in fact, human data are preferred.[2] Similarly, in developing Emergency Response Planning Guidelines (ERPGs), the American Industrial Health Association (AIHA) advocates use of human experience data as well as animal test data.[3] Inconsistently, in the Second Draft document, the worker exposure data provided by the Panel were used for AEGL-1 but not for AEGL-2 or AEGL-3.

The fact that PO exposure data is unpublished does not mean it should be disregarded. EPA states in its "Notice of Development of AEGLs" that relevant data are gathered from both private and public databases, not just published sources.[4] Also, the National Academy Press (NAS) treatise on developing AEGLs states that "all data sources should be consulted including the published scientific literature and any unpublished

---

2 "Guidelines for Developing Community Exposure Levels for Hazardous Substances," National Academy Press (1993), pp. 6, 78.

3 AIHA ERPG Committee: Concepts and Procedures for the Development of Emergency Response Planning Guidelines (Dec. 1992).

4 62 Fed. Reg. 58840 (Oct. 30, 1997).

information from industry and public sources. . . . Unpublished reports and individual expertise may be used to supplement published reports provided they are scientifically credible."[5]

Apparently the human exposure data was ignored in part due to misconception that sampling levels and exposure length were not available in the PO worker exposure reports. We are today providing supplemental information in Dr. Ripple's presentation demonstrating that PO exposure levels, sampling time and approximate duration are in fact known. Accordingly, such data should be used. These data would support a one-hour AEGL-2 of 312 ppm and a one-hour AEGL-3 of 1213 ppm.[6]

II. The Second Draft Fails to Give Due Weight to the 1995 Eldridge Report with Respect to Proposed AEGL-2

The Eldridge F344 rat data represents another significant instance where there has been a failure to incorporate available data (previously discussed in the Panel's comments to NAC/AEGL dated December 22, 1997). In the Eldridge study, F344 rats were exposed 6 hr./day five day/week via inhalation to 0-525 PO for 1 or 4 weeks following 1 week of exposure. The results demonstrate neither microscopic degeneration nor hyperplasia until 150 ppm. Eldridge's study involving microscopic histopathology has high reliability. This is a very health-protective check on the Panel's recommended AEGL-2 values because the response observed is less severe than the AEGL-2 criterion of "irreversible or other serious long-lasting effects", "impaired ability to escape", or "serious discomfort".

---

5 National Academy Guidelines, p. 23.

6 Based on human exposure data and application of formula $C^n \times t = K$ where $n = 1.2$ and UF of 3 for intraspecies variability.

III. Excessive Safety Factors Were Applied in Deriving AEGL-2 and AEGL-3 Factors Using the Mouse Data (NTP, 1985)

Unlike many chronic hazard exposure scenarios where appropriately a substantial safety factor is applied as a default assumption because humans may be more sensitive than rodents, for PO when calculating AEGL values it is inappropriate to do so.

As an obligate nose breather, the mouse is more sensitive to PO than humans because the mechanism of acute toxicity is site-of-contact nasal irritation. Target respiratory tissue in humans is greater than rodent target surface area because humans are not obligate nose breathers and have a larger target surface area. Humans are less sensitive to PO irritation based on human data indicating eye irritation following two weeks exposure at 300-500 ppm.[7]

Humans are expected to be less sensitive to rodents due to PO's expected detoxification pathways. In vitro metabolism studies indicate that humans demonstrate greater overall capacity for detoxification of PO, in particular for hydrolysis via epoxide hydrolase, the predicated predominant pathway in humans, and conjugation with glutathione via glutathione-S-transferases.[8] The second draft report fails to take into consideration these in vitro comparative metabolism data indicating that humans would not be more sensitive to PO effects than rodents.

A 10-fold safety factor is not warranted for either AEGL-2 or AEGL-3. With respect to AEGL-3, mice are more sensitive than humans as the mechanism of lethality appears to be suffocation following nasal obstruction based on irritant effect of PO on rodents.

---

[7] See CMA comments December 22.

[8] Fuller et al. (1998) (abstract).

Use of a three-fold safety factor is overprotective given that humans are less sensitive to PO than rodents and that the AEGL-3 values are based on a NOEL.

If the rodent data sets are selected, an AEGL-2 value of 223 ppm is appropriate for one hour based on Eldridge data (1995) applying a three-fold safety factor. An AEGL-3 value of 909 ppm is appropriate for one hour applying the NTP data (1985) and a three-fold safety factor.

IV. The Proposed PO AEGL-2 and AEGL-3 Values Are Not Justified by Reference to EO

The second draft takes comfort in the fact that the PO AEGLs are comparable to EO AEGLs. AEGLs are expected to be practical, achievable, cost-effective and soundly based on available scientific data. The second draft states at several points that EO is two-three times more toxic than PO yet justifies the AEGLs for PO by the level selected for EO. In fact, PO has neither the acute effect nor the chronic toxicity profile of EO. Relevant to AEGL-2, PO produces nasal irritation at the site of contact as well as nasal cell hyperplasia (Eldridge); in EO, there is only slight respiratory tract and eye irritation in rats at 1,000 ppm for four hours.[9] Systemic effects are observed for EO in lieu of site-of-contact irritation effects. With respect to chronic toxicity, PO, like formaldehyde, is a site-of-contact nasal carcinogen of relatively weak potency. In contrast, EO is a multi-site animal carcinogen.[10]

Relevant to setting AEGL-3 values, PO likely causes death in rodents at high exposures due to suffocation provoked by obstruction of the nasal passage following nasal irritation. In contrast, with respect to EO, the mechanism of lethality is described as lung

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[9] Embree et al. (1977).

[10] Golberg (1986).

edema and secondary lung infections, with no indication of nasal obstruction.[11] Thus the analogy to EO neither supports the AEGL-2 nor the AEGL-3 justification.

V. Extrapolations Should Be Rejected if They Fail to Meet AEGL Definitional Criteria

In the second draft, AEGLs are extrapolated for 30 minute, 1 hour, and 4 hour periods based on a rote calculation from 4 hour values used for AEGL-2 and -3. No AEGL value should be extrapolated which does not meet definitional criteria. Thus a one hour AEGL-2 that is back-calculated from an 4-hour value does not make sense if it is lower than needed to address serious long-lasting effects, impaired ability to escape or notable discomfort.

VI. The Second Draft is Inconsistent with the AIHA Emergency Response Planning Guidelines

While NAS is not bound by the AIHA ERPGs, it is instructive that the 1996 AIHA PO guidelines recommend an ERPG-3 of 750 ppm (one hour exposure without life-threatening effects); ERPG-2 of 250 ppm (one hour exposure without experiencing serious or irreversible health symptoms or impaired ability to escape); and an ERPG-1 of 50 ppm (one hour exposure without experiencing objectionable odor or other than mild transient adverse effects).

Conclusion

EPA has stated that ultimately AEGLs will be adopted as rules under the Clean Air Act and subject to judicial review. The Panel has previously commented that the Advisory Committee procedures on PO were flawed in that there has not been an adequate time to

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[11] Golberg (1986), citing Jacobsen et al. (1956).

review draft AEGL documents.[12] The AEGL Committee should avoid rushing out a final AEGL document that is not sound or feasible and consequently vulnerable on judicial review.

The science does not support the AEGL values proposed in draft 2. The science would support the values proposed here based on any of the following (one hour) values:

a) human data

312 ppm (AEGL-2)
1213 ppm (AEGL-3)

b) rodent data

223 ppm (Eldridge data – 3xUF)
909 ppm (NTP - 3xUF)

c) AIHA ERPGs

250 ppm (AEGL-2)
750 ppm (AEGL-3)

[12] Panel Comments to Dr. Paul Tobin, Nov. 24, 1997.

PRESENTATION TO THE NATIONAL ADVISORY COMMITTEE ACUTE EXPOSURE GUIDELINE LEVELS FOR PROPYLENE OXIDE

PREPARED BY THE PROPYLENE OXIDE PANEL OF THE CHEMICAL MANUFACTURERS ASSOCIATION (CMA) FOR PRESENTATION AT THE JUNE 8, 1998 MEETING IN WASHINGTON, DC

CMA Propylene Oxide Panel

Larry Andrews, Ph.D., D.A.B.T., Chair PO Panel
TRTG

Member companies:

ARCO Chemical Company
The Dow Chemical Company
Huntsman Corporation

Concerns Surrounding Discussion and Application of Toxicology Data* in the 2nd Draft of the PO AEGL Document

- **NAS treatise on developing AEGLs statement regarding Human Exposure/Experience Data:**
  "use of human data are preferred";
  "private, unpublished data accepted for this use".

- **AIHA "emphasizes human experience data to the extent data are available. However, this type of information is seldom available and, when available, usually gives only effects observed at either unknown or low levels of exposure *Therefore, animal test data often form the basis for these values, relying on acute inhalation tox with clinical observations and histopathology*." (Italics and underlining added)**

***Issues surrounding use of human data to be discussed by S. D. Ripple, representing the CMA PO Panel.**

Concerns Surrounding Discussion and Application of Toxicology Data* in the 2nd Draft of the PO AEGL Document

2nd draft AEGL-2

- **Substantive dataset on nasal irritation in rats not adequately considered (Eldridge *et al.*, 1995).**
- **Mechanism of toxicity for PO improperly assumed to be the same as for EO.**
- **Inappropriate safety factors applied to derivation of AEGL-2 values.**
- **Inconsistency in AEGL-2 values proposed for PO compared with the values set for EO.**

2nd draft AEGL-3

- **Inappropriate safety factors applied to derivation of AEGL-3 values.**
- **Mechanism of toxicity for PO improperly assumed to be the same as for EO.**
- **Inconsistency in AEGL-3 values proposed for PO compared with the values set for EO.**

2nd draft AEGL-2:

- **Substantive rat dataset not included in discussion of or determination of appropriate value for AEGL-2:**

Eldridge *et al.*(1995) determined the NOEL and LOEL for nasal irritation in rats following inhalation exposure to PO, based on microsopic histopathology and epithelial hyperplasia.

Respiratory epithelial hyperplasia NOEL = 50 ppm; LOEL = 150 ppm (5 x 6-hr exposures)

Microscopic olfactory degeneration NOEL = 150 ppm; LOEL = 525 ppm (5 x 6-hr exposures)

The **low severity** scores and **reliability of data** (microscopic histopathology) obviate any need for additional uncertainty factors, other than a very conservative 3 for intraspecies extrapolation. Using the NOEL/LOEL of 150 ppm and $C^n \times t = k$ (n = 1.2) and a conservative intraspecies SF of 3, the values would be:

AEGL-2 0.5 = 397 ppm; 1 hr = 223 ppm; 4 hr = 70 ppm; 8 hr = 39 ppm.

nd draft AEGL-2:

Mechanism of toxicity for PO not likely to be the same as for EO:

PO: site-of-contact effects, including nasal irritation and nasal cell hyperplasia (Eldridge *et al.*, 1995)

EO: systemic effects, (only slight respiratory tract and eye irritation noted at 1000 ppm for 4 hr; Embree *et al.*, 1977)

2nd draft AEGL-2:

• Inappropriate safety factors applied to derivation of AEGL-2 value:

Derivation of AEGL-2 was done using mouse data (dyspnea at 387 ppm; NTP, 1985), and safety factors (SF) of 3 for interspecies differences and 3 for intraspecies differences, for a total SF of 10.

* Humans are not more sensitive than rodents to irritating properties of PO:
Mouse = most sensitive species, with lowest NOEL/LOEL;

Sensitivity of mouse supported/explained by:
- the inferred mechanism (site-of-contact nasal irritation) ;
- dose/surface area differences (human = 2.79x rat target surface area);
- based on human data on irritation (documented as eye irritation following 2 weeks exposure to 300-1500 ppm).

Therefore do NOT need interspecies safety factor because humans are NOT more sensitive than rodents.

* Intraspecies SF of 3 applied for AEGL-2 represents very conservative approach:

overall capacity of humans for PO detoxication is equal to or greater than mouse or rat (based on *in vitro* metabolism data: Vmax/Km, Fuller *et al.*, 1998).

Maximum recommended total SF = 3, representing very conservative approach.

2nd draft AEGL-2:

• Inconsistency in AEGL-2 values proposed for PO compared with the EO values.

The clearly documented 2- to 3-fold greater toxicity of EO compared to PO was improperly translated to almost equivalent AEGL-2 values for EO and PO.

2nd draft AEGL-3:

• Inappropriate safety factors applied to derivation of AEGL-3 values.

Derivation of AEGL-3 values was done using mouse data (lowest NOEL for lethality of 4-hr 859 ppm; NTP, 1985), and SF of 3 for interspecies differences and 3 for intraspecies differences, for a total SF of 10.

* Humans are not more sensitive than rodents to the lethal properties of PO:
Mouse = most sensitive species, with lowest NOEL/LOEL

Sensitivity of mouse supported/explained by:
- the inferred mechanism of lethality being suffocation due to nasal obstruction following nasal irritation (site-of-contact nasal irritation) ;
- increased dose/surface area in rodents *vs* humans (human = 2.79 x rat target surface area) and -
- based on human data (documented minimum human NOEL for lethality = 380-1,500 ppm);

Therefore do NOT need interspecies safety factor because humans are NOT more sensitive than rodents.

* Intraspecies SF of 3 applied for AEGL-3 represents very conservative approach:
overall capacity of humans for PO detoxication is equal to or greater than mouse or rat (based on *in vitro* metabolism data: Vmax/Km, Fuller *et al.*, 1998).

Maximum recommended total SF = 3, representing very conservative approach, results in the following values:

AEGL-3 0.5 hr = 1620 ppm; 1 hr = 909 ppm; 4 hr = 286 ppm; 8 hr = 161 ppm.

2nd draft AEGL-3:

• Mechanism of toxicity for PO not likely to be the same as for EO:

PO: site-of-contact effects, including nasal irritation and nasal cell hyperplasia (Eldridge *et al.*, 1995).

Mechanism of lethality in rodents likely to be suffocation secondary to nasal obstruction due to nasal irritation, evidenced by nasal discharge, gasping and distended stomachs due to attempts by the obligate nose-breathers to breathe through the mouth.

EO: systemic effects, (only slight respiratory tract and eye irritation noted at 1000 ppm for 4 hr; Embree *et al.*, 1977).

Mechanism of lethality cited as lung damage, pulmonary edema, and secondary lung infections (Jacobsen *et al.*, 1956; Waite *et al.*, 1930; and Golberg, 1986). No indications of nasal obstruction.

2nd draft AEGL-3:

- Inconsistency in AEGL-3 values proposed for PO compared with the values set for EO.

The clearly documented 2- to 3-fold greater toxicity of EO compared to PO was improperly translated to almost equivalent AEGL-3 values for EO and PO.

Current 2nd Draft Proposed AEGL-2 and AEGL-3 Values (ppm):

	30 min	1 hr	4 hr	8 hr
AEGL-2	220	120	39	22
AEGL-3	490	270	86	48

CMA PO Panel Proposed* AEGL-2 and AEGL-3 Values (ppm):

	30 min	1 hr	4 hr	8 hr
AEGL-2	500	250	100	50
AEGL-3	1,000	750	280	150

****see Dec. 22, 1997 submission by the CMA PO Panel.**

CMA PO Panel Estimated AEGL-2 and AEGL-3 Values (ppm) Based on Animal Toxicity Data with a SF = 3:

	30 min	1 hr	4 hr	8 hr	
AEGL-2	397	223	70	39	(Eldridge *et al.*, 1995)
AEGL-3	1620	909	286	161	(NTP, 1985)

Human Exposure & Experience*

Issues for Consideration
Draft 2 Proposals for Propylene Oxide AEGLs

Susan D. Ripple, MS, MPH, CIH
CMA Propylene Oxide Panel

*Toxicology discussed separately by Larry Andrews, PhD, DABT

Use of Human Data

- There is inconsistent use of human exposure data in the Draft 2 Propylene Oxide AEGL proposal document
- Guidance from NAS and AIHA encourage the use of both human exposure data and animal toxicity data, which is available
- This presentation will apply human data to Propylene Oxide AEGLs with newly released sample and task duration information

Conflicting Use of Human Data
Draft 2 PO AEGL Proposal

Discussion of human data for:

- AEGL-1: cited and used
- AEGL-2: cited, but not used
- AEGL-3: cited, but not used

AEGL Committee & NAS
Use of Relevant Data

- **EPA states in its "Notice of Development of AEGLs":**
  - "relevant data are gathered from both private and public databases, not just published sources"[1]
- **National Academy Press (NAS) treatise on development of AEGLs states:**
  - "all data sources should be consulted including the published scientific literature and any unpublished information from industry and public sources... Unpublished reports and individual expertise may be used to supplement published reports provided they are scientifically credible."[2]
  - "the use of human data are preferred"(id. at 6.78)

[1] 62 Federal Register 58840 (Oct. 30, 1997)
[2] "Guidelines for Developing Community Exposure Levels for Hazardous Substances," National Academy Press (1993), p. 23

AIHA "Approach to Developing ERPGs"

- "emphasizes human experience data to the extent data are available. However, this type of information is seldom available and, when available, usually gives only effects observed at either unknown or low levels of exposure. Therefore, animal test data often form the basis for these values, relying on acute inhalation tox with clinical observations and histopathology."[1]

  - In the case of PO, human data as well as animal toxicity data are available and should be considered
  - Human exposures were high and quantified and are available
  - Acute inhalation toxicity data with clinical evaluation and histopathology are available for AEGL-2 and AEGL-3 values (indicates lethality was triggered by suffocation)

[1] American Industrial Hygiene Association: ERPG Committee "Concepts and Procedures for the Development of Emergency Response Planning Guidelines (ERPGs) pg. 5 (December 1992)

"Facility 1" Human Exposure Data[1] during Drumming Operations*

(revised June 8, 1998)

Sample No.	Activity Description	Sampling Duration (min)	PO Concentration (ppm)[a]
1	Breathing zone of operator during drumming of PO; local ventilation fan turned on	177	380
2	Same location as Sample #1 but local exhaust ventilation fan turned off for about 5 minutes	171	1520
3	Same as Sample #2	124	1310
4	Same as Sample #2 & #3	121	525
5	Same location as samples #1 - #4, but fan had been turned back on and had been running about five minutes	135	392
6	Same as Sample #5	116	460

[1] Submitted November 1997 by CMA PO Panel to AEGL Committee

* Typical drumming operation duration = 7 hours

Human Data Available for Consideration in Development of PO AEGL-2

- Using "Facility 1" data[1], human exposures between **380** and 1,500 ppm (3-hour sample time)[2] during drumming operations were associated with an AEGL-2 type endpoint of eye irritation

Proposed AEGL-2 Value based on Human Exposure Data:

- based on 380 ppm for 2.95 hours sample time, ($C^n \times t = k$ where n=1.2, and SF of 3 for intraspecies variability) a 1-hour AEGL-2 of **312 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997
[2] New information submitted by CMA PO Panel on June 8, 1998

Human Data Available for Consideration in Developing PO AEGL-3

- Using "Facility 1" data[1], human exposures up to **1,520 ppm** for 2.85 hours sample time[2], during drumming operations, were not associated with lethality
  - minimum NOEL for lethality in humans = 1520 ppm for 2 .85 hours

Proposed AEGL-3 Value based on Human Exposure Data:

–based on 1520 ppm for 2.85 hours sample time, ($C^n \times t = k$ where n=1.2, and SF of 3 for intraspecies variability) a 1-hour AEGL-3 of **1213 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997
[2] New information submitted by CMA PO Panel on June 8, 1998

CMA PO Panel Estimated AEGL-2 and AEGL-3 Values (ppm) Based on Human Data* with SF=3

	30 min	1 hr	4 hr	8 hr	
AEGL-2	556	312	98	55	(380 ppm; 2.95 hr)
AEGL-3	2161	1213	382	214	(1520 ppm; 2.85 hr)

*see Dec. 22, 1997 submission, supplemented by additional data on June 8, 1998, by the CMA PO Panel

Summary

- We have shown you new information which clarifies the human exposure data submitted in November 1997
- Given that human data are to be used, and human exposure data is available, AEGLs should consider this data

Conclusions

- The science does not support the values currently proposed in the AEGL Draft 2
- Science would support either of the following:
  - the values based on human data, or
  - the values based on appropriate rodent endpoints with appropriate safety factors
- AEGLs calculated from appropriate animal data with appropriate safety factors support AEGL values calculated from human data

Human Exposure & Experience*

Issues for Consideration

Draft 2 Proposals for Propylene Oxide AEGLs

Susan D. Ripple, CIH

CMA Propylene Oxide Panel

*Toxicology discussed separately by Larry Andrews, PhD, DABT

Use of Human Data

- There is inconsistent use of human exposure data in Draft 2 Propylene Oxide AEGL proposed document
- Guidance from NAS and AIHA encourage use of both human exposure data and animal toxicity data which is available
- This presentation will apply human data to Propylene Oxide AEGLs with newly released sample and task duration information

Conflicting Use of Human Data
Draft 2 PO AEGL Proposal

Discussion of human data for:

- AEGL-1: cited and used
- AEGL-2: cited, but not used
- AEGL-3: cited, but not used

AEGL Committee & NAS
Use of Relevant Data

- **EPA states in its "Notice of Development of AEGLs":**
  - "relevant data are gathered from both private and public databases, not just published sources"[1]
- **National Academy Press (NAS) treatise on development of AEGLs states:**
  - "all data sources should be consulted including the published scientific literature and any unpublished information from industry and public sources. . . Unpublished reports and individual expertise may be used to supplement published reports provided they are scientifically credible."[2]
  - "the use of human data are preferred"(id. at 6.78)

[1] 62 Federal Register 58840 (Oct. 30, 1997)

[2] "Guidelines for Developing Community Exposure Levels for Hazardous Substances," National Academy Press (1993), p. 23

AIHA "Approach to Developing ERPGs"

- "emphasizes human experience data to the extent data are available. However, this type of information is seldom available and, when available, usually gives only effects observed at either unknown or low levels of exposure. Therefore, animal test data often form the basis for these values, relying on acute inhalation tox with clinical observations and histopathology."[1]

  - In the case of PO, human data as well as animal toxicity data are available and should be considered
  - Human exposures were high and quantified and are available
  - Acute inhalation toxicity data with clinical evaluation and histopathology are available for AEGL-2 and AEGL-3 values (indicates lethality was triggered by suffocation)

[1] American Industrial Hygiene Association: ERPG Committee "Concepts and Procedures for the Development of Emergency Response Planning Guidelines (ERPGs) pg. 5 (December 1992)

Additional Human Exposure Information

- Defined sampling duration for Facilty 1 Environmental Health survey (~3 hours)
- Defined typical drumming operation duration (7 hours)
- Defined sample analysis method for Facility 1 (gas phase chromatography)

"Facility 1" Human Exposure Data[1] during Drumming Operations*

(revised June 8, 1998)

Sample No.	Activity Description	Sampling Duration (min)	PO Concentration (ppm)*
1	Breathing zone of operator during drumming of PO; local ventilation fan turned on	177	380
2	Same location as Sample #1 but local exhaust ventilation fan turned off for about 5 minutes	171	1520
3	Same as Sample #2	124	1310
4	Same as Sample #2 & #3	121	525
5	Same location as samples #1 - #4, but fan had been turned back on and had been running about five minutes	135	392
6	Same as Sample #5	116	460

[1] Submitted November 1997 by CMA PO Panel to AEGL Committee

* Typical drumming operation duration = 7 hours

Human Data Available for Consideration in Development of PO AEGL-2

- Using "Facility 1" data[1], human exposures between **380** and 1,500 ppm (3-hour sample time)[2] during drumming operations were associated with an AEGL-2 type endpoint of eye irritation

Proposed AEGL-2 Value based on Human Exposure Data:

  - based on 380 ppm for 2.95 hours sample time, ($C^n \times t = k$ where n=1.2, and UF of 3 for intraspecies variability) a 1-hour AEGL-2 of **312 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997
[2] New information submitted by CMA PO Panel on June 8, 1998

Human Data Available for Consideration in Developing PO AEGL-3

- Using "Facility 1" data[1], human exposures up to **1,520 ppm** for 2.85 hours sample time[2], during drumming operations, were not associated with lethality
  - minimum NOEL for lethality in humans = 1520 ppm for 2 .85 hours

Proposed AEGL-3 Value based on Human Exposure Data:

–based on 1520 ppm for 2.85 hours sample time, ($C^n \times t = k$ where n=1.2, and UF of 3 for intraspecies variability) a 1-hour AEGL-3 of **1213 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997

[2] New information submitted by CMA PO Panel on June 8, 1998

Summary

- We have shown you new information which clarifies the human exposure data submitted in November 1997
- Given that human data are to be used, and human exposure data is available, AEGLs should consider this data

Summary of Proposed AEGL Values for Acrolein					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	Eye irritation,"annoyance"/ discomfort in humans (Weber-Tschopp et al., 1977)
AEGL-2 (Disabling)	0.2 ppm (0.46 mg/m^3)	0.2 ppm (0.46 mg/m^3)	0.1 ppm (0.23 mg/m^3)	0.1 ppm (0.23 mg/m^3)	≥25% Decrease in respiratory rate and sensory irritation in humans (Weber-Tschopp et al., 1977)
AEGL-3 (Lethality)	1.98 ppm (4.5 mg/m^3)	1.40 ppm (3.2 mg/m^3)	0.70 ppm (1.6 mg/m^3)	0.50 ppm (1.15 mg/m^3)	1 hr. no-effect-level for death in rats (Ballantyne et al., 1989)

Attachment 12

AEGL-1 FOR ACROLEIN (ppm [mg/m^3])				
AEGL Level	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**0.03 [0.07]**	**0.03 [0.07]**	**0.03 [0.07]**	**0.03 [0.07]**

Species: Human
Concentration: 0.09 ppm
Time: Varied: 5-35 min.
Endpoint: Threshold for annoyance/discomfort and eye irritation
Reference: Weber-Tschopp et al., 1977

Uncertainty Factor = 3

Intraspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between individuals)

Temporal Extrapolation: Values were flat-lined across time since minor irritation is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect

Supporting data: *Odor threshold in sensitive persons = 0.03-0.034 ppm*

Exposure Regimens (Weber-Tschopp et al., 1977)

1) Continuous exposure at steadily increasing concentrations

   - 31 men, 22 women
   - Acrolein concentration from 0 to 0.60 ppm
   - Duration of 40 minutes with increasing concentration for the first 35 minutes, then 0.60 ppm for the final 5 minutes

2) Several Exposures of short duration at continuously increasing concentrations

   - 17 men, 25 women
   - Acrolein concentrations 0, 0.15, 0.30, 0.45, and 0.60 ppm
   - Duration of 1.5 minutes at each concentration with a recovery period of 8 minutes between exposures

3) Longer exposure at a constant acrolein concentration

   - 21 men, 25 women
   - Acrolein concentration of 0.3 ppm
   - Duration of 60 minutes

Subjective Effect Thresholds in Human Volunteers Exposed to Acrolein

"Annoyance"	0.09 ppm
Eye Irritation	0.09 ppm
Nose Irritation	0.15 ppm
Doubling of Blinking Rate	0.26 ppm
10% Decrease in Respiratory Rate	0.3 ppm
Throat Irritation	0.43 ppm
25% Decrease in Respiratory Rate	0.6 ppm

Subjective Effects in Human Subjects Exposed to 0.3 ppm Acrolein

Effect	% of Subjects after 10 minutes	% of Subjects after 20 minutes
Wish to leave room	50	72
Moderate eye irritation	18	35
Severe eye irritation	3	18
Moderate Nose Irritation	7	19
Severe nose irritation	1	4
Moderate throat irritation	1	2
Severe throat irritation	0	1
Doubling of blinking rate	66	70
0% decrease in espiratory rate	47	60

AEGL-2 FOR ACROLEIN (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	0.2 [0.46]	0.2 [0.46]	0.1 [0.23]	0.1 [0.23]

Species: Human
Concentration: 0.6 ppm
Time: Varied: 5-35 min.
Endpoint: ≥25% decrease in respiratory rate and sensory irritation
Reference: Weber-Tschopp et al., 1977

Uncertainty Factor = 3

Intraspecies = 3 (mechanism appears to be irritation and is not expected to vary greatly between individuals)

Modifying Factor = 2 (4-hr and 8-hr time points only)

Apparent adaptation/desensitization to higher acrolein concentrations may be due in part to sensory nerve damage

Temporal Extrapolation: Values were flat-lined across time since minor irritation is generally a threshold effect and prolonged exposure is not likely to result in a greatly enhanced effect

AEGL-3 FOR ACROLEIN (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	1.98 [4.5]	1.40 [3.2]	0.70 [1.6]	0.50 [1.15]

Species: Rat
Concentration: 14 ppm
Time: 1 hour
Endpoint: No-effect-level for death
Reference: Ballantyne et al., 1989

n = 2

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (mechanism is irritation and is not expected to vary greatly between species)

Intraspecies = 3 (mechanism is irritation and is not expected to vary greatly between individuals)

Summary of Proposed AEGL Values for Acrolein					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	0.03 ppm (0.07 mg/m^3)	Eye irritation,"annoyance"/ discomfort in humans (Weber-Tschopp et al., 1977)
AEGL-2 (Disabling)	0.2 ppm (0.46 mg/m^3)	0.2 ppm (0.46 mg/m^3)	0.1 ppm (0.23 mg/m^3)	0.1 ppm (0.23 mg/m^3)	≥25% Decrease in respiratory rate and sensory irritation in humans (Weber-Tschopp et al., 1977)
AEGL-3 (Lethality)	1.98 ppm (4.5 mg/m^3)	1.40 ppm (3.2 mg/m^3)	0.70 ppm (1.6 mg/m^3)	0.50 ppm (1.15 mg/m^3)	1 hr. no-effect-level for death in rats (Ballantyne et al., 1989)

ACGIH TLV-TWA: 0.1 ppm

ACGIH TLV-STEL: 0.3 ppm

NIOSH IDLH: 5 ppm

NIOSH REL-TWA: 0.1 ppm

OSHA PEL-TWA: 0.1 ppm

PEL-STEL: 0.3 ppm

ERPG-1: 0.1 ppm
ERPG-2: 0.5 ppm
ERPG-3: 3 ppm

Acute Exposure Values for Peracetic Acid

ORNL Staff Scientist: Kowetha A. Davidson

Chemical Manager: Mark McClanahan

Secondary Reviewers: George Rogers &
John S. Morawetz

NAC/AEGL, June 8-10, 1998, Washington, DC

Attachment 13

Physical/Chemical Characteristics

- CAS No. – 79-21-0
- Chemical formula – CH_3COOH
- Molecular Wt. – 76.05
- Physical state – colorless liquid
- Characteristics – mixture containing up to 40% PAA, acetic acid, H_2O_2, H_2SO_4, and stabilizer
- vapor press. – 14.5 mm Hg @ 25°C
- Solubility – freely soluble in H_2O
- Odor – no data
- Unstable – decomposes to synthetic constituents

Uses

- Disinfectant against bacteria, fungi, and viruses
- Bleaching agent
- Polymerization catalyst or co-catalyst
- Epoxidation of fatty acid esters
- Epoxy resin precursor
- Synthesis of other chemicals

Human Toxicity

- Corrosive/irritant agent
- Data for concentrations ≤5ppm
- Lacrimation at 5 ppm
- Extreme or unbearable discomfort or nasal irritation at 2–5 ppm
- Slight discomfort to nose or eyes at 1–1.5 ppm
- Mild to tolerable discomfort at 0.5–1.0 ppm
- no discomfort at ≤0.5 ppm

Animal Toxicity

- Corrosive/irritant agent
- LC_{50} = 153 ppm (1 h); 65 ppm (4 h) – rat;
- 164 to 168 ppm (1 h) – mouse
- Effects observed at lethal concentrations
  - extreme respiratory tract irritation
  - transient weight loss
  - lung consolidation, edema, and hemorrhage

Animal Toxicity (Cont..)

- Non-lethal effects
- 55–189 ppm for 15–90 min
  - Clinical signs indicative of respiratory irritation
  - Transient weight loss
  - Slight to severe nasal lesions (squamous metaplasia of turbinates and epithelial atrophy of dorsal meatus)

Animal Toxicity (Cont.)

- 3.3–14.3 ppm for 25 min
  - 28–64.7% decrease in respiratory rate
  - no gross or microscopic lesions
- 71–169 ppm for 25 min
  - 71–74% decrease in respiratory rate
  - lacrimation, nasal discharge, lung edema & inflammation, transient decrease in weight gain

Derivation of AEGL-1

30 min	1 hour	4 hours	8 hours
1.0 ppm	0.5 ppm	0.17 ppm	0.17 ppm

- Endpoint: mild irritation
- UF = 1 (human sensitivity)
- Reference: Fraser & Thorbinson, 1986; McConagh, 1997

Derivation of AEGL-2

30 min	1 hour	4 hours	8 hours
1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm

- Endpoint: irritation
- UF = 1 (human sensitivity)
- Reference: Fraser & Thorbinson, 1986

Derivation of AEGL-3

30 min	1 hour	4 hours	8 hours
9.2 ppm	6.7 ppm	3.6 ppm	2.6 ppm

- Endpoint: lethality (LC_{01} = 20 ppm (1 hour exposure)
- UF = 3 (species sensitivity)
- Reference: Janssen, 1989a

Proposed AEGL Values

Class.	30 min	1 hr	4 hrs	8 hrs	Endpoint/Reference
AEGL-1	1.0 ppm	0.5 ppm	0.17 ppm	0.17 ppm	mild irritation/ Fraser & Thorbinson, 1986; McDonagh, 1997
AEGL-2	1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm	irritation/ Fraser & Thorbinson, 1986
AEGL-3	9.2 ppm	6.7 ppm	3.6 ppm	2.6 ppm	lethality (LC01)/ Janssen, 1989a

TOXICITY OF NO

Methemoglobin formation

Conversion to NO_2

TOXICITY OF NO_2

Irritation

Pulmonary edema

EXOGENOUS SOURCES OF NO AND NO_2

Auto exhaust

Electric utilities

Industrial boilers

Gas stoves

Unvented space heaters

Kerosene heaters

Wood stoves

Tobacco products

ATMOSPHERIC REACTIONS

$2NO + O_2 \rightarrow 2NO_2$
(minor at ambient temp)

$NO + O_3 \rightarrow NO_2 + O_2$

$NO + HO_2\cdot \rightarrow NO_2 + HO\cdot$

$NO + RO_2\cdot \rightarrow NO_2 + RO\cdot$

$NO_2 + HO\cdot \rightarrow HNO_3$

$2NO_2 \rightleftarrows N_2O_4$

- temperature dependent
- favors NO_2 production

Calculated Time to Reach 5 ppm NO_2	
NO conc. in 20% O_2	**Time**
80 ppm	3 min
20 ppm	>1 hr

NITRIC OXIDE DATA PENDING

Dogs and rats: Concentration-response data for MetHb formation

80-640 ppm for 6 hr

controlled for NO_2 formation

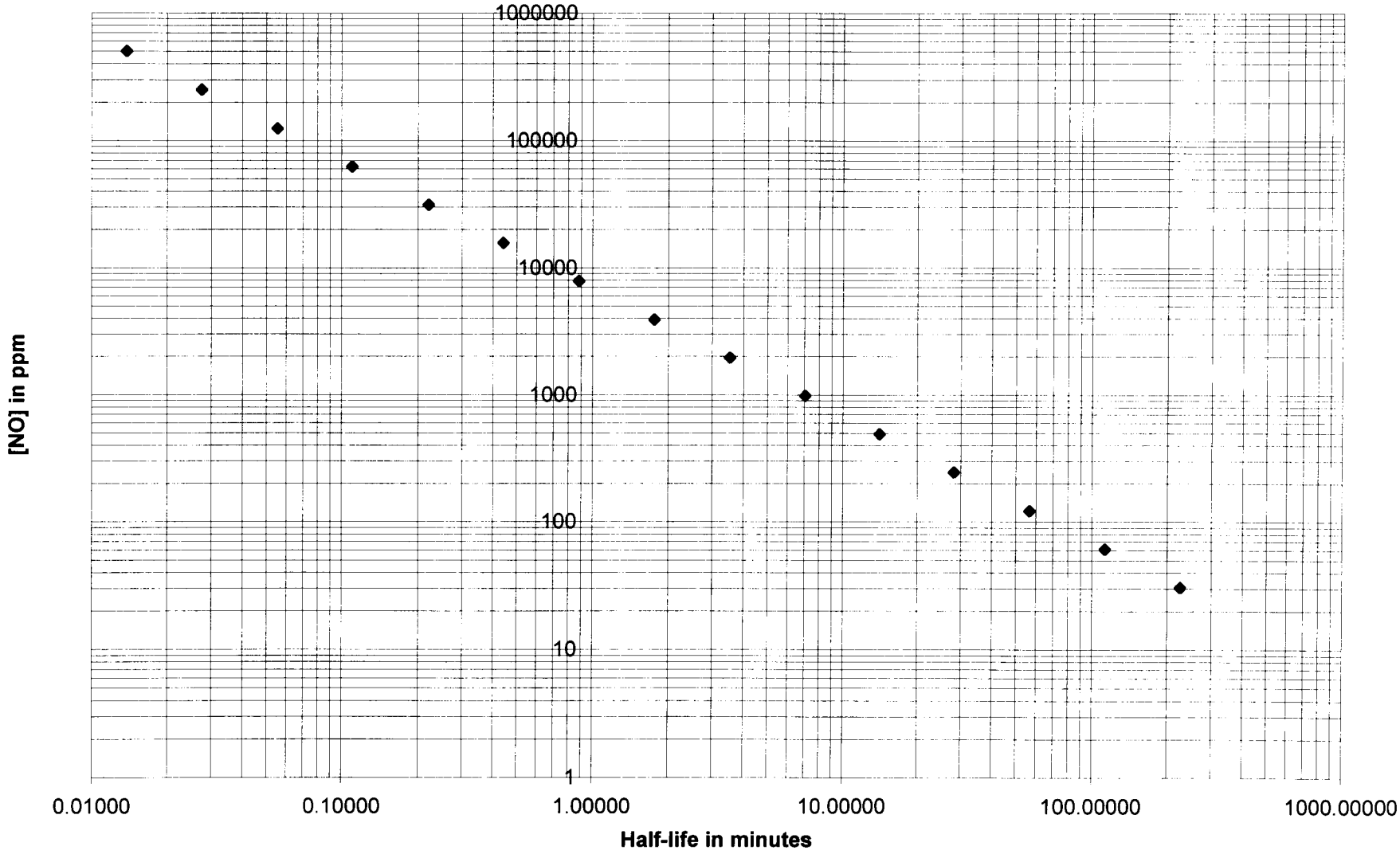
Expected for incorporation by September meeting

Possible use for AEGL-2 and -3 derivations (currently no data available)

RECOMMENDATIONS

- Derive AEGL values for NO_2 at Sept. meeting
- Derive AEGL values for NO at Sept. meeting
- Add NO_2 Executive Summary as an appendix to the NO TSD
- Include in the NO TSD that NO_2 is also of concern, but exact amount is impossible to predict

Half-life of NO in Atmospheric Air



Attachment 15

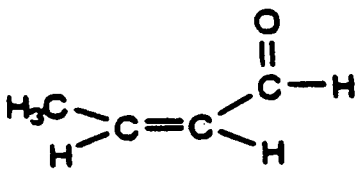
$$[NO_2] = k_A[NO] + k_B[NO]^2[O_2] + k_C t[NO]^2[O_2]$$

$[NO_2]$	in ppm
$[NO]$	in ppm
$[O_2]$	in percentage
t	in seconds (contact time)

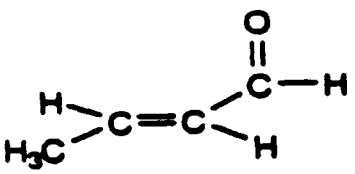
k_A	5.12×10^{-3}
k_B	4.41×10^{-6}
k_C	0.86×10^{-5}

SLIDE #1

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CROTONALDEHYDE



Cis isomer



Trans isomer

ORNL Staff Scientist: *Sylvia Milanez*
Chemical Manager: *Doan Hansen*
Chemical Reviewers: *George Alexeeff and Larry Gephart*

SLIDE #2

Table 2. Human short-term exposure toxicity data			
Exposure conc. (ppm)	Exposure time	Endpoint; Notes	Reference
0.035 - 0.2 0.037-1.05 0.12	sec.	Odor thresholds mostly from secondary sources	Verschue.,'96 Ruth, 1986 Amoore 1983
0.038	sec. ?	Several exposures/subject	Tepikina, 1997
0.17	1 min.	Odor detection/irritation; exposure through mask; conc.?	Trofimov, 1962
0.56 (1.1)	**< 8 hr**	**Occasional eye irritation; brief excursions to 1.1 ppm**	**Fannick, 1982***
4.1	15 min (10 min?)	Marked resp. irritation; lacrimation in ~30 s; exp to cigarettes?	Sim & Pattle 1957
3.5-14 3.8	sec? 10 s	Irritation to wake sleeper "Irritating in 10 sec."; no details	Fieldner et al., 1954
7.3	sec?	Sharp odor, strong eye and nose irritation; no expt. details	Dalla Vale & Dudley, 1939
8 14 (nose) 19 (eyes)	sec?	Irritation threshold; how define "irritation" unknown	Ruth, 1986 Amoore 1983 Amoore 1983
15	< 30 s	Lab w. "sniffed;" odor strong, not intolerable; no eye discomfort.	Rinehart, 1967
45-50	< 30 s	"Sniffing:" odor pungent; burning sens. of conjunct.; no lacrimation	Rinehart, 1967

***Study used for derivation of AEGL-1.**

SLIDE #3

TABLE 6. AEGL-1 for Crotonaldehyde UF =3 (sensitive humans)				
30 min	**1 hr**	**4 hrs**	**8 hrs**	**Endpoint (Reference)**
0.19 ppm [0.53 mg/m^3]				Mild eye irritation, exp. <8 hrs to 0.56 ppm (Fannick, 1982)

SLIDE #4

TABLE 10. Alternate AEGL-1 for crotonaldehyde (ppm) UF = 3 Scaling: $C^{1.2} \times t = k$				
30 min	**1 hr**	**4 hrs**	**8 hrs**	**Reference**
0.77 0.55	0.43 0.31	0.14 0.10	0.08 0.05	15-min (Sim & Pattle, 1957) 10-min
1.1	0.59	0.19	0.10	Fannick, 1982
0.19*	**0.19***	**0.19***	**0.19***	**Fannick, 1982 - "flat-line"**
0.14 0.42 1.4	0.08 0.24 0.80	0.02 0.06 0.20	0.01 0.03 0.10	0.01 RD_{50} (Steinhag., 1984) 0.03 RD_{50} - geom. mean 0.1 RD_{50}

***Proposed AEGL-1 value.**

Sim and Pattle, 1957. Men exposed to 4.1 ppm for 10 or 15 min had marked respiratory irritation; lacrimation; smoking allowed.

Fannick, 1982. Occupational exposure to 0.56 ppm crotonaldehyde for < 8 hrs. caused occasional eye irritation.

Steinhagen and Barrow, 1984. RD_{50} = 4.2 ppm (mean for Swiss-Webster and $B6C3F_1$ mice).

SLIDE #5

TABLE 5. Pulmonary responses of rats exposed to 10-580 ppm crotonaldehyde for 5 minutes to 4 hours (data from Rinehart, 1967)

Conc. x time range (ppm-min)	Geometric mean conc. x time	No. animals	CO uptake rate (% pre-exposure ± SD)	Ether uptake rate (% pre-exposure ± SD)
Controls	0	12	99.5 ± 12.5	103.1 ± 12.8
1000-2000	1330	12	92.9 ± 9.0	94.8 ± 9.4
2000-4000	2730	12	89.9 ± 5.6**	92.8 ± 5.7*
4000-8000	5390	12	86.7 ± 11.3**	91.0 ± 14.9*
8000-16,000	10,940	12	73.3 ± 12.8**	81.2 ± 9.6**
16,000-32,000	21,430	10	58.3 ± 10.8**	67.0 ± 9.2**
16,000-32,000 (animals died)	28,900	4	< 40	<40

Significantly different from controls: *$p \leq 0.10$ **$p < 0.05$

- Proliferative respiratory bronchiole lesions were found 3 days after exposure above 8000 ppm-min. Edema was seen only where death occurred within 24 hrs.
- Concentration and time were ~similarly important for toxicity.

SLIDE #6

TABLE 7. AEGL-2 for Crotonaldehyde				
30 minutes	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
6.4 ppm [9.2 mg/m^3]	3.6 ppm [5.2 mg/m^3]	1.1 ppm [1.6 mg/m^3]	0.64 ppm [0.92 mg/m^3]	Rat prolif. bronchiole lesions, ~20-40% lower gas uptake (Rinehart,1967)

Scaling: $C^{1.2} \times t = k$
UF = 30 (3 for sensitive humans; 10 for interspecies)

SLIDE #7

TABLE 11. Alternate AEGL-2 values for crotonaldehyde (ppm)						
30 min	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**MF**	**Reference**
1.4	0.79	0.25	0.14	3	-	0.1 x mouse RD_{50}
4.2	2.4	0.75	4.2	3	-	0.3 x RD_{50} - geom. mean
14	7.9	2.5	1.4	3	-	1 x mouse RD_{50} (Steinhagen & B., 1984)
6.4*	3.6*	1.1*	0.64*	30	-	**8000 ppm-min→20-40% dec. in rat gas uptake rates; bronchiolar prolif. lesions (Rinehart, 1967)**
6.4	3.6	1.1	0.64	10	3	
19	11	3.4	1.9	10	-	
13	7.1	2.2	1.3	10	-	**5390 ppm-min→up to 25% lower rat gas uptake**

***Proposed AEGL-2 value.**

SLIDE #8

TABLE 3. Acute lethality (LC_{50} data) of crotonaldehyde inhalation exposure in animals			
Species	Exposure time	LC_{50}	Reference
Rat	30 min.	1400 ppm	Skog, 1950
Rat	3 min.	"saturated" (~40,000 ppm)	Smyth & Carpenter, 1944; Smyth, 1966
Rat*	**5 min. 10 min. 15 min. 30 min. 60 min. 4 hrs**	**3132 ppm 1480 ppm 809 ppm 593 ppm 391 ppm 88 ppm**	**Rinehart, 1967* (LC_{50} values calc. by probit analysis)**
Rat	4 hrs	70 ppm	Voronii et al., 1982
Mouse	2 hrs	530 ppm	Trofimov, 1962
Mouse	2 hrs	200 ppm	Voronii et al., 1982
Guinea pig	30 min. 15 min.	1000 ppm 2000 ppm	Smyth, 1966

***Study used to derive AEGL-3 values.**

SLIDE #9

TABLE 4. Mortality of rats exposed to crotonaldehyde vapor for 5-240 minutes (Rinehart, 1967)

5 min. ppm–mort.	10 min. ppm–mort.	15 min. ppm–mort.	30 min. ppm–mort.	60 min. ppm–mort.	240 min. ppm–mort.
1920 – 0/5	800 – 1/12	550 – 0/10	370 – 0/10	370 – 4/10	50 – 1/10
2420 – 1/5	1110 – 4/12	680 – 2/10	420 – 2/10	400 – 6/10	60 – 2/10
2680 – 1/5	1380 – 6/12	750 – 5/10	530 – 4/10	490 – 7/10	70 – 4/10
3180 – 3/5	1820 – 7/12	850 – 7/10	675 – 6/10	590 – 7/10	100 – 6/10
4160 – 4/5	2050 – 9/12	980 – 7/10	800 – 8/10	640 – 10/10	120 – 8/10
4640 – 5/5		1090 – 8/10	890 – 9/10		200 – 9/10
		1290 – 10/10			
LC_{50}=3132	LC_{50}= 1480	LC_{50} = 809	LC_{50} = 593	LC_{50} = 391	LC_{50} = 88
LC_1=1492	LC_1 = 440	LC_1 = 419	LC_1 = 268	LC_1 = 138	LC_1 = 26

SLIDE #10

TABLE 8. AEGL-3 for Crotonaldehyde				
30 minutes	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
26 ppm [75 mg/m^3]	13 ppm [38 mg/m^3]	4.2 ppm [12 mg/m^3]	0.64 ppm [0.92 mg/m^3]	Rat LC_1 for 30-min or 1-hr exposure (Rinehart, 1967).

Scaling - for ½ and 1 hour: use LC_1 directly
Scaling - for 4 and 8 hours: $C^{1.2} \times t = k$
UF = 10 (3 for sensitive humans, 3 for interspecies)

SLIDE #11

TABLE 12. Alternate AEGL-3 values for Crotonaldehyde (ppm) Scaling: $C^{1.2} \times t = k$ UF = 10					
30 min	**1 hr**	**4 hrs**	**8 hrs**	**Endpoint (Reference)**	
47	26	8.3	4.6	Rat 30-min LC_{50} =1400 ppm; LT = ⅓ (LC_{50}). Nose secretion, gasping, lacrimation, lung hemorrhage (Skog, 1950)	
38	21	6.7	3.7	50-60% lower CO and ether uptake rates; prolif. bronchiole lesions from 16,000 ppm-min]. (Rinehart,1967)	
38	22	6.9	3.9	LC_{10}	**Rat 30-min or 1-hr exp. (Rinehart, 1967)**
26*	**13***	**4.2***	**2.3***	**LC_1**	
13	7.4	2.3	1.3	Rat 4-hr LC_{50} =70 ppm; LT = ⅓ (LC_{50}). No expt. details. (Voronii et al., 1982)	
21	12	3.7	2.1	Mouse 2-hr LC_{50} = 200 ppm; LT = ⅓ (LC_{50}). No expt. details (Voronii, 1982)	
56	31	9.9	5.6	Mouse 2-hr LC_{50} =530 ppm; LT = ⅓ (LC_{50}). Res. distress, excitation, lung hemorrhage,edema. (Trofimov, 1962)	
33	19	5.9	3.3	Guinea pig 30-min. LC_{50} = 1000 ppm; LT = ⅓ (LC_{50}). Expt. details not given. (Smyth, 1966)	

LT = lethality threshold ***Proposed AEGL-3 value.**

SLIDE #12

SUMMARY OF PROPOSED AEGL VALUES FOR CROTONALDEHYDE (ppm [m/m^3])					
Classification	30 min	1 hr	4 hrs	8 hrs	Endpoint (Reference)
AEGL-1	0.19 [0.53]	0.19 [0.53]	0.19 [0.53]	0.19 [0.53]	Human eye irritation (Fannick, 1982)
AEGL-2	6.4 [9.2]	3.6 [5.2]	1.1 [1.6]	0.64 [0.92]	Rat bronchiole lesions, impaired pulmonary function (Rinehart, 1967)
AEGL-3	26 [75]	13 [38]	4.2 [12]	2.3 [6.7]	Rat LC_1 for 30-min or 1-hr exp. (Rinehart, 1967).

SLIDE #13

Using Mouse RD_{50} to Derive AEGL-1 and AEGL-2 Values

- Good correlation between **0.01-0.1 x RD_{50}** and TLVs for 19/23 chemicals with TLV of 0.02-1000 ppm. One exception was formaldehyde, which is chemically related to crotonaldehyde: **(0.03 x RD_{50}** vs. TLV was **0.10 vs. 2 ppm**). (Alarie, 1981)

- The ACGIH replaced the TLV of 2 ppm with a **ceiling limit of 0.3 ppm** for formaldehyde in 1992 (based on extensive data) and for crotonaldehyde in 1998 (for consistency with formaldehyde).

Predicted responses in humans at multiples of mouse RD_{50} values			
Multiple of RD_{50}	Responses/ Possible effects	Permitted exposure	Corresponding AEGL level*
10	Severe injury/ lethality	Minutes	N/A
1	Intolerable to humans/ tissue damage	Hours	N/A
0.1	Some sensory irritation/ pharmacological rxn.	Hours - days	AEGL-2
0.03	**Geometric mean of 0.01 and 0.1**	**??**	**??**
0.01	No sensory irritation/ no physiological effects	Weeks - years	AEGL-1
0.001	No effect of any kind on respiratory system	Years, continuously	N/A

N/A = not applicable

$$Ni(CO)_4 \underset{k_2}{\overset{k_1}{\longleftrightarrow}} Ni(CO)_3 + CO$$

$$Ni(CO)_3 + O_2 \xrightarrow{k_3} Ni(CO)O + CO + CO_2$$

$$\tau = 1/k_1 + k_2[CO]/k_1 k_3[O_2]$$

NICKEL CARBONYL AEGL

Presentation Overheads

National Advisory Committee for
Acute Expsoure Guideline Levels for Hazardous Substances

Meeting No. 10
Old Post Office, M09

June 8-10, 1998

PROPOSED AEGL VALUES FOR NICKEL CARBONYL (ppm [mg/m^3])					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NA	NA	NA	NA	not appropriate; toxicity may occur in the absence of detection; AEGL-1 data unavailable
AEGL-2					
AEGL-3	0.32 [2.2 mg/m^3]	0.22 [1.5 mg/m^3]	0.11 [0.76 mg/m^3]	0.08 [0.55 mg/m^3]	estimated lethality threshold using mouse lethality data of Kincaid et al., (1953); UF=10 (3 for interspecies [larger species less susceptible] and 3 for intraspecies variability); n=2

AEGL-1

- Quantitative data unavailable
- Odor threshold: 0.5 - 3.0 ppm
- Adverse effects at or below odor detection
- Human volunteers exposed to "whiffs" of 0-5 ppm (Sunderman 1990)
  - recognition responses erratic
  - no exposure duration provided
- AEGL-1 not recommended

AEGL-2

- **Quantitative data in humans unavailable**

- **Animal data**
  - **developmental toxicity in rats and hamsters**

MALFORMATIONS IN RATS FOLLOWING 15-MINUTE GESTATIONAL EXPOSURE TO NICKEL CARBONYL DURING GESTATION							
Observation	Group A	Group B	Group C	Group D	Group E	Group F	Group G
Exposure (mg/L)	sham	CO	0.16 (22.4 ppm)	0.30[a] (42 ppm)	0.08 (11.2 ppm)	0.16	0.16
Exposure day	8	7	7	7	8	8	9
Live fetuses/litter	9.2±2.1	8.3±2.6	8.1±2.6	9.1±1.6	7.6±3.6	8.3±2.6	7.4±4.8
Live fetuses/ conceptuses	110/114	187/215‡	113/135‡	91/100†	121/134†	108/120†	96/112†
Mean fetus wt. (g)	3.4±0.2	3.1±0.7	3.0±0.3‡	3.0±0.4‡	3.3±0.5	3.1±0.3‡	3.2±0.3‡
Litters with malformed fetuses	0/12	0/22	9/14*	9/10*	2/16	9/13*	0/13
Total malformations[b]	0	0	15*	29*	2	19*	0

a Only 10 of 19 dams lived to day 20

b Ocular malformations: bilateral anophthalmia, unilateral anophthalmia, bilateral microphthalmia, unilateral microphthalmia, anophthalmia and microphthalmia; only one incidence each in the Group C and Group D was categorized as other than ophthalmic anomalies. † $p<0.05$; ‡ $p<0.01$; * $p<0.001$

TERATOGENIC EFFECTS OF NICKEL CARBONYL INHALATION (8.4 ppm, 15 min/day) IN PREGNANT SYRIAN HAMSTERS		
Parameter	**Control**	**$Ni(CO)_4$-treated**
Total malformations[a] day 4 exposure day 5 exposure	0% (0/9)	5.5% (8/146)* 5.8% (10/171)*
Proportion of litters with malformed fetuses day 4 exposure day 5 exposure	0% (0/9)	33% (4/12)* 24% (4/17)*
Serous cavity hemorrhage day 4 exposure day 5 exposure	0% (0/9)	18% (26/146)* 25% (42/171)*

a Included 9 fetuses with cystic lungs, 7 fetuses with exencephaly, 1 fetus with exencephaly plus fused rib, and 1 fetus with anophthalmia plus cleft palate; for fetuses of dams exposed on days 6 or 7, there was 1 fetus with fused ribs and 2 fetuses with hydronephrosis.

* Significantly different from controls ($p<0.05$)

AEGL-2 Values for Nickel Carbonyl
Based Upon Developmental Toxicity Data

30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
0.079 ppm	0.056 ppm	0.028 ppm	0.019 ppm	reduction in live fetuses/conceptus in rats (11.2 ppm; n = 2) exposed for 15 min on g.d. 8 (Sunderman et al., 1979);UF = 100: 10 for interspecies; 10 for intraspecies
0.16 ppm	0.11 ppm	0.056 ppm	0.004 ppm	reduction in live fetuses/conceptus and mean fetus wt. in rats (~~11.2~~ 22.4 ppm; n = 2) exposed for 15 min on g.d. 7 (Sunderman et al., 1979);UF = 100: 10 for interspecies; 10 for intraspecies
0.059 ppm	0.042 ppm	0.02 ppm	0.015 ppm	teratogenic effects in hamsters; 15-min exposure to 8.4 ppm on g.d. 4 or 5; (Sunderman et al., 1980); UF = 100: 10 for interspecies; 10 for intraspecies

AEGL-3

- **Quantitative data in humans limited**

- **Animal data**
  - **lethality data (LC_{50}) for four species**
  - **sensitivity inversely proportional to body mass**

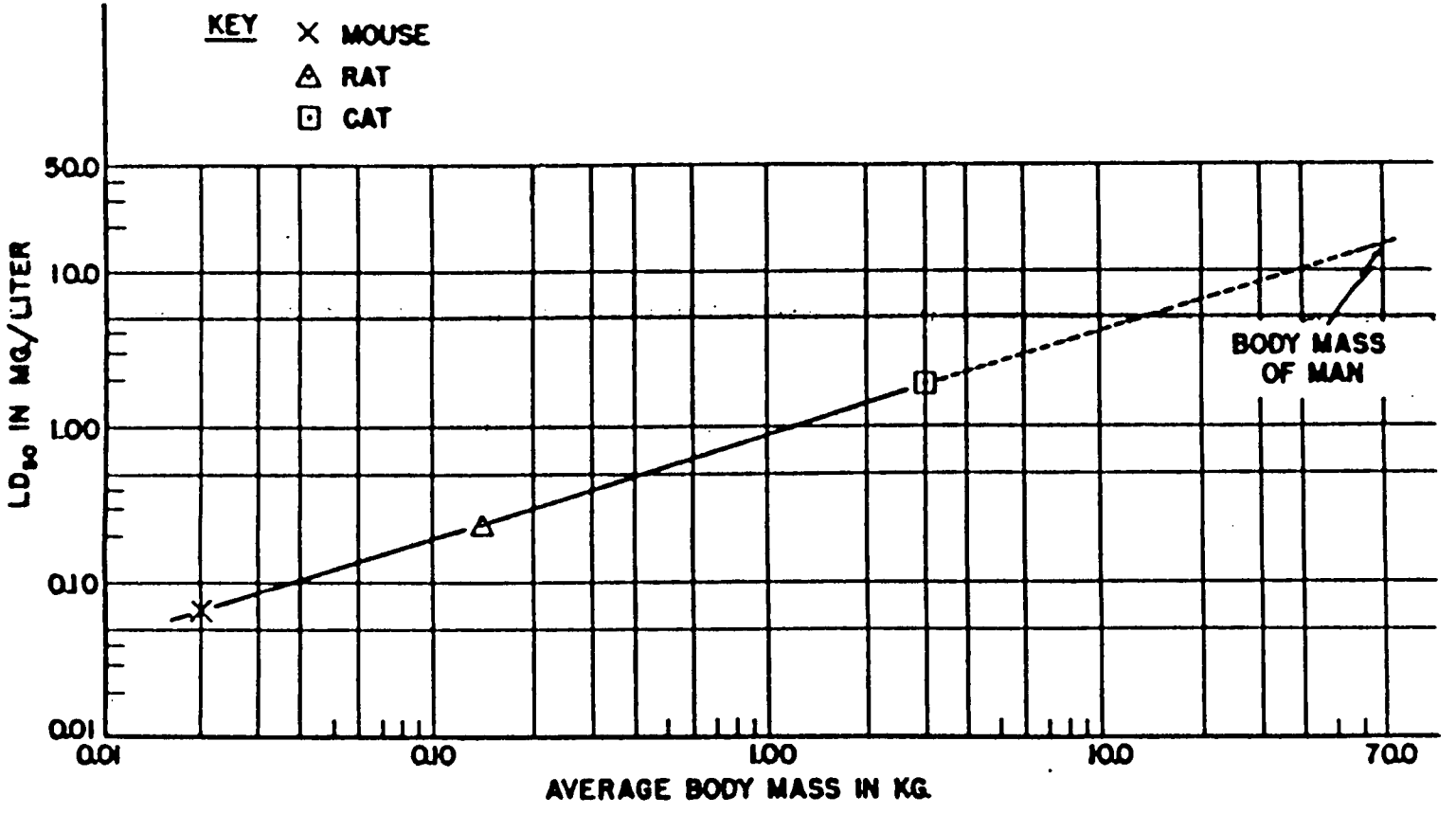
- **Mouse most sensitive**

- **Data unavailable for calculating *n* for $C^n \times t = k$; default to $n = 2$**

- **Uncertainty factors**
  - **3 for intraspecies variability**
  - **3 for interspecies variability**

ISSUES

- **Data deficiencies for AEGL-1**
- **Data deficiencies for AEGL-2**
- **Uncertainty factor application**
  - **UF of 3 for interspecies variability**
    - **body mass - toxicity relationship**
    - **epidemiologic studies (long-term exposure to 0.072 ppm - not life threatening)**
- **Half-life of nickel carbonyl in ambient air**
  - **AEGL values for longer times appropriate ?**



Relationship between the L.D.$_{50}$ and the size of three experimental animals.

Kincaid et al., 1953

Attachment 19

Exposure Guideline Levels for Nickel Car

NAC/AEGL meeting Washington

Comments and Presentation

Dr Sally Pugh Williams

Acute Exposure Guideline Levels for Nickel Carbonyl

NAC/AEGL meeting Washington

Comments and Presentation

Dr Sally Pugh Williams
Occupational Health Services Manager, INCO Europe Ltd.
June 1998

Acute Exposure Guideline Levels (AEGLs) for Nickel Tetracarbonyl.

Comments prepared by
Dr. Sally Pugh Williams Occupational Health Services Manager
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May 1998

Background

Accidental releases of Extremely Hazardous Substances (EHSs) through transport spills, industrial accidents may pose a hazard to the general public with potential for injury being mainly by an inhalational risk. Inhalational exposure limits for emergency exposures to hazardous substances may be useful for emergency planning committees/public health controls where individuals may have a once in a lifetime exposure. The U.S. Environmental Protection Agency (U.S.EPA) [(1)] has identified 366 EHSs based on acute lethality data in rodents. Whilst these substances may have adequate toxicity information in experimental animals, few have adequate toxicity data from human studies.

Established exposure limits in the workplace or ambient air quality may be available but these are often not easily translated into the kinds of limits required for emergency exposures. Three acute exposure guidelines levels (AEGLs) can be developed for emergency exposures, referenced to 4 exposure time periods: 30 mins; 1 hour; 4 hours; and 8 hours . These are distinguished by varying degrees of severity of toxic effects; it is also recognised that most emergency exposures will rarely exceed 1 hour in practice.

With respect to Nickel Tetracarbonyl, which is a listed EHS, the AEGL-3 exposure value is being considered by the United States Environmental Protection Agency (U.S.E.P.A.) .
An acute exposure guideline level -3, (AEGL-3) is defined as follows:-

- AEGL-3 is the airborne concentration (expressed in ppm or mg/m^3) of a substance at or above which it is predicted that the general population, including 'susceptible' but excluding ' hypersusceptible' individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

The criteria and methods used to develop an AEGL need close examination . These are described by the Committee on Toxicology National Research Council [(2)], and take into consideration the following factors:

- the population potentially exposed, this means the general population, including the susceptible but not necessarily the hypersusceptible

- the degree and pattern of exposure; the duration and concentration of exposure should reflect realistic scenarios for accidents involving the release of EHSs, including stored inventories, location, dispersion and weather.
- the nature, reversibility and severity of the anticipated effect; acute health effects (including mortality), pulmonary effects and possibly long term effects.
- proportion of the population who are subject to toxic effects; because of individual susceptibility, adequate safety factors need to be built in.

When evaluating a chemical such as Nickel Tetracarbonyl, additional factors need to be considered, particularly its decomposition time under appropriate release scenarios, as this will determine the dose available for potential health effects in humans.

The Draft AEGL-3s are based on an estimated lethality threshold in mice. In humans there is a lack of definitive quantitative lethality data , necessitating the use of safety factors in calculating the proposed levels, however other considerations are necessary.

- Special attention should be given to the acute exposure guideline level reference time periods, for their appropriateness, in relation to the ability of Nickel Tetracarbonyl to "produce" an acute lethal dose due to its decomposition, not only in the air, but also in the body.
- The biological consequences of an acute exposure to Nickel Tetracarbonyl in humans needs to be reviewed, because of the lack of quantitative relationship between air levels of Nickel Tetracarbonyl and any consequent illness in exposed persons. Biological monitoring should be considered as an additional tool for exposure assessment and for prediction of adverse health outcome.
- A further consideration needs to be given to measuring any proposed level in the ambient air for risk evaluation purposes.

Sources and production of Nickel Tetracarbonyl.

Detailed information about Nickel Tetracarbonyl production, storage and use in the USA is not available in the draft document but there are no Nickel Tetracarbonyl refineries in the U.S.A.. Limited experimental use may be found in research laboratories; Nickel Tetracarbonyl may also be used as a carbonylating agent or catalyst in organic chemistry synthesis. The potential to form Nickel Tetracarbonyl from nickel catalysts in the presence of carbon monoxide at low temperatures is well known and incidents of accidental formation and release of Nickel Tetracarbonyl still occur. Potential release scenarios from all known Nickel Tetracarbonyl operations would be helpful in focusing risk assessments. This is not addressed in the draft document, but is noted as a criterion for setting AEGLs.

In evaluating potential hazards, experience from Nickel Tetracarbonyl refinery operations maybe helpful, and this will be described more fully.

The Nickel Tetracarbonyl Reaction and its Decomposition Characteristics.

Nickel Tetracarbonyl is an intermediate in the carbonyl refining of nickel. This method of nickel refining, also called the "Mond" process after its inventor, is a vapometallurgical process whereby a direct reaction occurs between finely divided nickel and carbon monoxide at relatively low temperatures:

$$Ni+4CO = Ni(CO)_4$$

This reaction is reversed by heating the Nickel Tetracarbonyl to above 450K, forming pure nickel and regenerating the carbon monoxide [3]. At the Clydach Nickel Refinery, both the formation and decomposition reactions are carried out at close to atmospheric pressure. At INCO's Sudbury Nickel Refinery in Canada and at a Russian refinery, the formation reaction is carried out at high pressure.

Factors affecting the decomposition of Nickel Tetracarbonyl within the process e.g. the effect of temperature and catalysis, are well understood by the refinery operators. We know of only one published experimental work on the decomposition of Nickel Tetracarbonyl in air (Stedman) [4]. The results agree well with the work performed by the Clydach Nickel Refinery chemists. In the absence of carbon monoxide, the lifetime of up to 100ppb of Nickel Tetracarbonyl in air at 296K (24C) and atmospheric pressure, is reported as 60 seconds. The most important single factor affecting this lifetime is the presence of carbon monoxide, which significantly increases the lifetime of Nickel Tetracarbonyl in air. As the concentrations of carbon monoxide rise, this then begins to pose another health hazard due to toxic effects of carbon monoxide. It is therefore important to understand whether the Nickel Tetracarbonyl is "pure", for example from a liquid carbonyl source, or whether it is present in carbon monoxide containing Nickel Tetracarbonyl gas. (See graph).

Factors such as Dispersion and Dose.

From a given Nickel Tetracarbonyl source, dispersion, dilution and decomposition will occur in the air, all of which affect the potential dose that may reach the general population at risk of exposure. The duration of human exposure will also be limited by these factors.

When assessing the acute exposure guideline levels for Nickel Tetracarbonyl , the dose may be derived from the acute animal toxicity data, but additional consideration must be given to the reference periods for exposure, based on the decomposition characteristics of Nickel Tetracarbonyl in air under realistic release scenarios.

For health protection against acute lethal effects then the short term exposure levels should advise 30min, or 1hour reference periods. Scenarios where an acute lethal dose for humans could actually be delivered for longer periods of time i.e. 4 or 8 hours, would be extremely unlikely; unless information on the sources, use and production of Nickel Tetracarbonyl in the U.S.A., and associated historical accident profile dictates otherwise.

Detection

In carbonyl refinery operations process controls are paramount to ensure complete enclosure of the operation due the extremely toxic nature of Nickel Tetracarbonyl. A system of Nickel Tetracarbonyl leak detectors is constantly monitoring the atmosphere of the plants as well as special lamps for leak detection.

Currently, the U.K. Occupational Exposure Standard for Nickel Tetracarbonyl is a Short term exposure limit (STEL) 0.24mg/m^3 or 0.1ppm as Nickel, over a 15 min reference period [5].

This is based on the acute lethality consideration. An 8 hour limit has not been deemed appropriate for the acute lethal effect.

The plant environmental monitoring alarms at the Clydach refinery, are set at 80ppb. The "Miran" multi-point sampler uses infra-red measurement and is sensitive to as low as 10ppb and has provided remarkably good protection. Altogether 70 sampling heads are situated at strategic points in the carbonyl areas of the plants. At the INCO Sudbury carbonyl refinery, a chemiluminescence detection system is in place with a sensitivity of 0.1ppb.

In terms of detection in the atmosphere however, specialised dedicated equipment is needed for the **rapid** detection of ppb quantities of Nickel Tetracarbonyl e.g. gas chromatography, long path length infra-red spectrophotometry or chemiluminescent reaction detection. These require considerable expertise and expense. There are no reliable hand held devices or easily portable devices.

Biological effect in humans acutely exposed to Nickel Tetracarbonyl.

One of the most important factors in terms of human health protection is the lack of quantitative data to give a dose-response relationship between acute Nickel Tetracarbonyl exposure and adverse health effects based on ambient air level measurements. The paper of Vuopala [6] does not give full consideration of the chemistry of Nickel Tetracarbonyl, and therefore the human lethal concentrations may not be accurate. There is well documented evidence however, describing the acute consequences of occupational inhalational exposures.

Experience at the INCO Clydach Tetracarbonyl Nickel refinery, which is a continuous process operating 365 days a year, shows that since its opening in 1902, there have been 6 fatal cases (1904-4; 1932-1; 1937-1). World literature reviews show that since the gas was discovered that there have been 20 reported fatalities due to Nickel Tetracarbonyl exposure world-wide [7].

In Clydach, in the period 1925-1950 there were approximately 4 lost time accidents per year related to Nickel Tetracarbonyl exposure; 2.5 per year between 1950 and 1980, with the exception of 25 men in a serious incident reported in 1958. Since 1990 there have been a total of 7 lost time accidents (lost time = more than 3 days off work).

These figures are important in relation to the production of Nickel Tetracarbonyl in the refinery where about 450 tonnes of Nickel Tetracarbonyl are produced per day. None of the Nickel Tetracarbonyl is stored, the only Nickel Tetracarbonyl present at any time is as an intermediate between the two stages of the process, amounting to less than 1 tonne.

Whilst this may not be the case in all situations where there is Nickel Tetracarbonyl, this again raises the question about the importance of knowing sources of Nickel Tetracarbonyl as a factor in establishing AEGLs.

Understanding of the toxicokinetics of Nickel Tetracarbonyl, together with experience at the Clydach Nickel refinery, confirms the usefulness of biological monitoring i.e. urinary nickel measurements in those possibly exposed to Nickel Tetracarbonyl. The 8 hour post exposure urinary nickel level as described by Sunderman [8] may correlate with the delayed pulmonary effects of an acute exposure to Nickel Tetracarbonyl. This then can determine whether prophylactic chelation therapy is administered. Studies of the distribution and metabolism of Nickel Tetracarbonyl in the body also show dissociation of Nickel Tetracarbonyl, so that steady state systemic levels of Nickel Tetracarbonyl in the body are unlikely for any significant time, due to intracellular decomposition to nickel and carbon monoxide [9]. Therefore, the temporal scaling equation used to derive the AEGL-3 which is applicable for other systemically acting vapours, may not be correct in the case of Nickel Tetracarbonyl.
In accident release situations, in the absence of reliable correlation between air levels and biological effect, difficulties in the rapid measuring of levels , then the ability to check nickel in urine in any persons possibly exposed at the appropriate time post exposure should be noted. Skilled advice will be necessary to evaluate the results.

Animal toxicity [1,10,11]

This will not be discussed in detail. However, the species variability for acute lethal effect of acute Nickel Tetracarbonyl exposure is noted as is the relationship between lethality and body weight .This latter observation has not been recorded in human cases and its relevance to man is queried.

Rationale and proposed AEGL-3

The paper of Vuopala [6] is questioned in relation to the data it gives on the decomposition and dose of Nickel Tetracarbonyl relevant to acute lethal effects in humans as discussed above.
The AEGL-3 levels recommended have little value in terms of public health protection and would be difficult to measure in the acute situation as well as accurately; to ensure no exposure occurred then biological monitoring of those potentially exposed using urinary nickel evaluation with interpretation from trained experienced practitioners

may be a prudent recommendation. Evaluation of the sources, uses, and handling of Nickel Tetracarbonyl is essential to ensure adequate vigilant workplace control of these processes . This should then ensure minimal risk to the General population from accidental release of Nickel Tetracarbonyl.

Conclusion

Hazard identification shows that in humans and animals, Nickel Tetracarbonyl is acutely lethal, and has severe life threatening consequences for adverse acute health effects. However, the dose-response relationship is dependent on the decomposition characteristics of Nickel Tetracarbonyl in the atmosphere and in the body. This should not be ignored in setting appropriate Acute Exposure Guideline Levels.
Full evaluation of the uses and sources of exposure to Nickel Tetracarbonyl are warranted to help determine appropriate short term exposure levels under realistic accident scenarios. Biological monitoring is a useful additional method of health protection.
Methods of ambient air detection for Nickel Tetracarbonyl are feasible, but not practicable for emergency use.

References.

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3. Ullmann's Encyclopedia of Industrial Chemistry Vol A 17 Nickel Compounds VCH 1991
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6. Nickel Tetracarbonyl Poisoning report of 25 cases U. Vuopala, E. Huhti, J. Takkunen and M. Huikko Annals of Clinical Research 2: 214-222, 1970
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9. The distribution and metabolism of Nickel Tetracarbonyl in mice Agneta Oskarsson and H. Tjalve British Journal of Industrial Medicine 1979, 36,326-335
10. Toxicity review 19 The toxicity of nickel and its inorganic compounds Health and Safety Executive 1987 ISBN 0 11 883961 6
11. IPCS Environmental Health Criteria 108 Nickel World Health organisation 1991 ISBN 92 4 157108X

Nickel Tetracarbonyl

Dr. WILLIAMS
INCO EUROPE LIMITED

Nickel Tetracarbonyl- Questions?

- Can protective ambient air levels be set, when decomposition is taken into account?
- Can these levels be measured in Emergency situations?
- A Biological monitoring recommendation should be considered to ensure adequate health assessment of exposure?
- Sources of Nickel Tetracarbonyl - planned and accidental?

Nickel Tetracarbonyl

- History
- Health Effects
- Dispersion, Dilution, Decomposition, Dose
- Detection
- Sources
- Public Health Protection- biological monitoring

Nickel Tetracarbonyl

History

Health Effects

History of Nickel Refining - early experiments

- Ludwig Mond
- Carl Langer
- 1890 Problems with the production of Bleach lead to the discovery of an unknown compound
- Nickel carbonyl $Ni(CO)_4$ gas

History of Nickel refining -- Pilot Plant--Clydach refinery

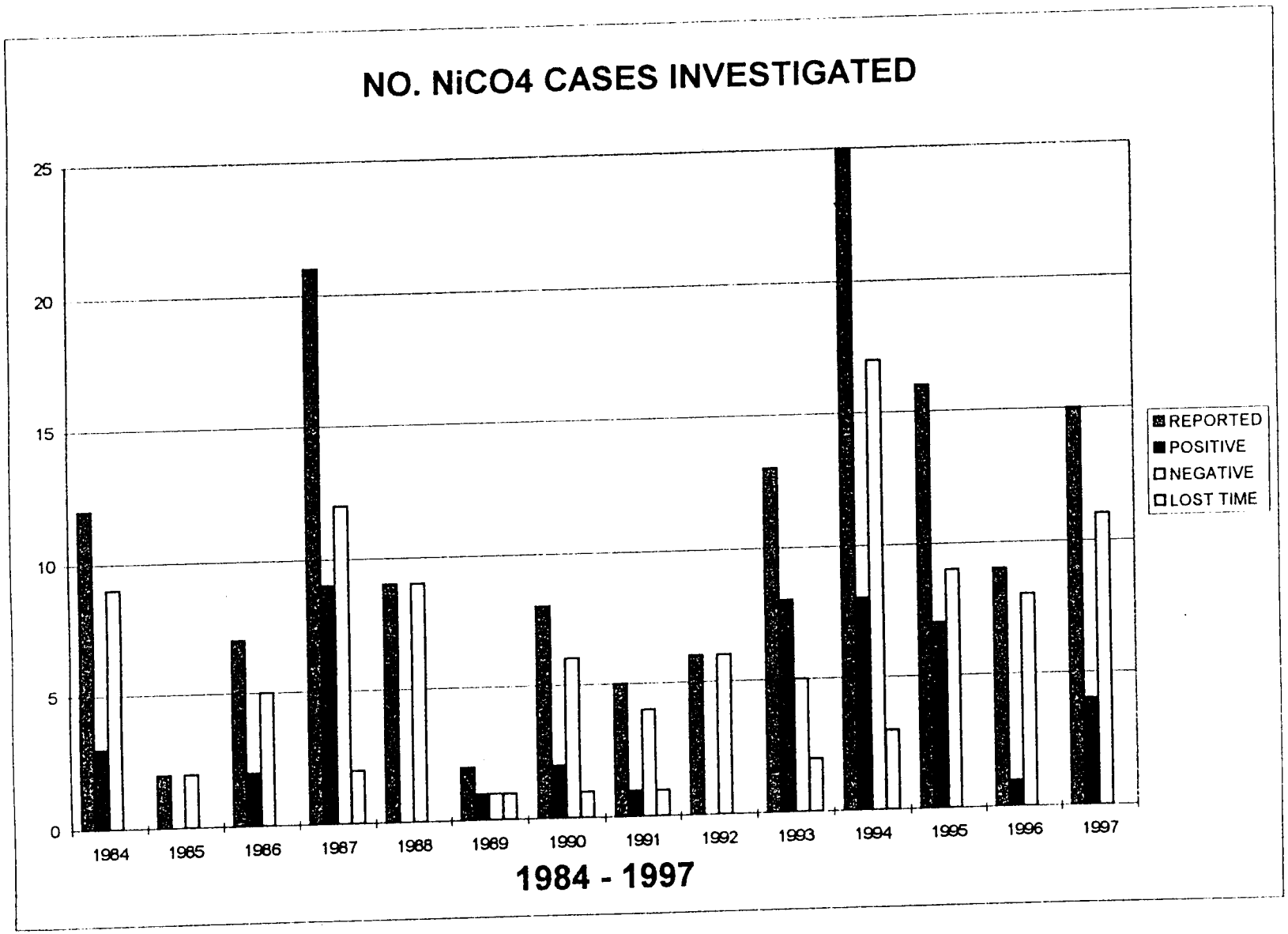
- 1892 Birmingham Henry Wiggin refinery
- Feb 12 1900 Clydach
- high grade anthracite
- water supply
- Swansea docks- import and export capability
- Skilled local workforce

Toxicity of Nickel Carbonyl

- 6 fatal cases
- 4 in 1901
- 1 in 1932
- 1 in 1937

Toxicity of Nickel Carbonyl

- case studies
- 1925-1950 4 lost time cases per annum
- 1950-1980 2.5 lost time cases per annum
- 1958 25 lost time cases per annum
- 1980-1990 4 lost time cases in 10 years
- 1991-1997 6 lost time cases


NO. NiCO4 CASES INVESTIGATED
25
20
15
10
5
0
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
REPORTED
POSITIVE
NEGATIVE
LOST TIME
1984 - 1997

Sources of Nickel Tetracarbonyl

planned production and handling

unplanned production

Nickel Tetracarbonyl

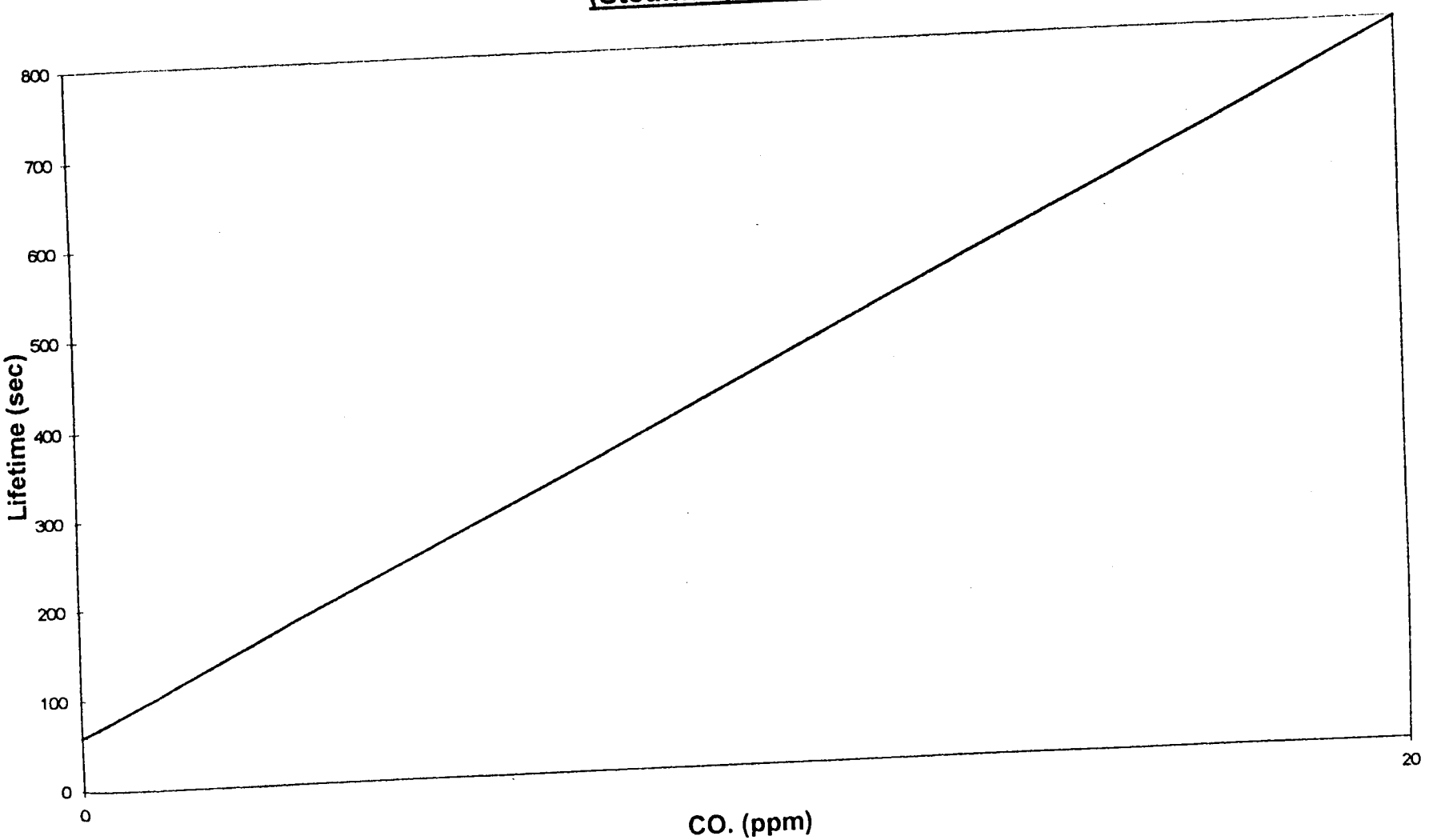
Dispersion, dilution, decomposition, dose

Detection

Dispersion, dilution, decomposition, dose

- Characteristics of Nickel Tetracarbonyl
- in air, in gaseous form, in liquid form
- Dose and Potential for acute toxic effects
- distribution and metabolism in the body

Dependence of Lifetime of ppb Levels of Nickel Carbonyl in Air on Presence of CO. (Stedman, extrapolated)



Detection

- lack of correlation between air levels and acute toxic effects in humans
- practicalities of air measurements
- biological monitoring-exposure, health effect and treatment

Public Health Protection- Nickel Tetracarbonyl

- Hazard assessment
- Risk
- Control

INCO Material Safety Data Sheet

** THIS DATA SHEET IS PREPARED IN COMPLIANCE WITH DIRECTIVE 91/155.EEC**

Gaseous Nickel Carbonyl
Process Intermediate

THIS DATA SHEET IS FOR USE ON THE INCO CLYDACH NICKEL REFINERY

1. Chemical Composition and Company Identification

Nickel Carbonyl
C.A.S. Number 13463-39-3
EINECS Number 236-669-2

Carbon Monoxide
C.A.S. Number 211-128-3
EINECS Number 630-08-0

INCO Europe Ltd.
Clydach Refinery
Clydach
Swansea
SA6 5QR

Emergency Tel. No.
222

2. Composition

Typical Analysis

$Ni(CO)_4$	CO
0.001-90%	Balance

Information on Ingredients

Hazardous Ingredients	Typical Composition	STEL[(1)] ! mg/m^3	STEL[(1)] ! ppm
Nickel Tetracarbonyl	0.001-90%	0.24*	0.1
Carbon Monoxide	Balance	330	300

! 15 min reference period, short term exposure limit
* as Ni

3. Hazards Identification

F: R11 Highly flammable
Carc. Cat. 3: Category 3 carcinogen
R40 Possible risk of irreversible effects
Repr. Cat. 2 Toxic to reproduction category 2
R61 May cause harm to the unborn child
T+; R26 Very toxic by inhalation
S53 Avoid exposure - obtain special instruction before use

S45 In case of accident or if you feel unwell seek medical advice immediately (Show label where possible)

Refer to MSDS for carbon monoxide for details on carbon monoxide. This data sheet only deals with nickel carbonyl.

Ingestion	No data available
Inhalation	Very toxic by inhalation.
Skin Contact	No data available
Eye Contact	No data available
Environment	No information available. Atmospheric decomposition generates nickel oxide and carbon monoxide.
Physical	Highly flammable

4. First Aid Measures

FOLLOW INCO EUROPE NICKEL CARBONYL PROTOCOL, CONTACT OCCUPATIONAL HEALTH IMMEDIATELY

Ingestion	Not applicable.
Inhalation	SEEK MEDICAL ATTENTION IMMEDIATELY.
Skin	Not applicable.
Eyes	Not applicable.

5. Fire Fighting Measures

Wear approved air fed breathing apparatus.
Extinguish fires by isolating source of gas.
Nickel carbonyl fires generate inhalable nickel oxide a Cat. 1 Carcinogen
Cool surrounding equipment with water spray.

If practical any fire involving nickel carbonyl should be allowed to burn in order to dispose of the nickel carbonyl.

6. Accidental Release

Wear approved air fed breathing apparatus.
Extinguish all flames.
Control leak by isolating source of gas.

7. Handling and Storage

Process intermediate only encountered in plant designed and approved to contain nickel carbonyl/carbon monoxide gas mixtures.

8. Exposure Controls / Personal Protection

For exposure limits see Section 2.
Maintain airborne nickel carbonyl levels as low as possible. Do not inhale.
Continuous ambient air monitoring for nickel carbonyl should be used in all buildings were nickel carbonyl is present.

9. Physical and Chemical Properties

Colourless gas. Has a musty smell.

Ingredient	Mol. Wt.	Magnetic Properties
$Ni(CO)_4$	170.73	N/A
CO	28	N/A

Viscosity	Not known
Freezing point	N/A
Boiling point	N/A
Flash Point	Not known
Autoflammability	Flammable
Explosive properties	Explosive with Air
Vapour pressure	N/A
Density	7.62g/ml
Particle size	N/A
Solubility	Insoluble in water
Partition coefficient	N/A

N/A Not Applicable

10. Stability and Reactivity

Flammable gas.
Decomposes on heating with formation of carbon monoxide possible increase in pressure unless container is vented.
Decomposes on exposure to air.
Atmospheric decomposition generates nickel oxide.

11. Toxicological Information [2,3,4]

The most important route of absorption into the body is via inhalation. There are no data on the effects after gastrointestinal exposure; although nickel carbonyl is lipid soluble and could penetrate the skin, dermal toxicity has not been demonstrated.

Studies in animals and humans confirm the acute toxicity of nickel carbonyl in the lungs. Renal excretion of nickel being the major route of elimination. The carbon monoxide moiety is excreted through the lungs.
The acute poisoning effects in humans have been described as occurring in two phases; immediate and delayed. The immediate symptoms include frontal headache, vertigo, nausea, vomiting, insomnia and irritability which may be followed by an asymptomatic period before the onset of delayed symptoms resembling that of a viral pneumonia. Urinary nickel concentrations are a guide to the extent of exposure and the likelihood of pulmonary complications, particularly the 8 hour post exposure urinary nickel.
A medical management protocol is available at INCO Occupational Health and should be consulted immediately. In severe cases death has occurred with widespread tissue damage being noted including cerebral oedema and haemorrhage reported between the third and fourteenth day post exposure. Treatment may be advised with the chelating drug Antabuse which augments nickel excretion, corticosteroids may also be indicated.
Long term low dose exposure in humans rarely results in asthma, pulmonary infiltrations and eosinophilia. EEG abnormalities have also been reported in one study and a decrease in monoamine oxidase activity. There has been no evidence of cancer in humans but tumours have been demonstrated in animals following inhalational studies and intravenous dosage. Experiments in animals via inhalation and injection of nickel carbonyl in pregnant rats have shown birth defects in the offspring including anopthalmia, micropthalmia, cystic lungs and hydronephrosis; these effects have not been seen in humans working with nickel carbonyl.

12. Ecological Information

Do data available.

13. Disposal Information

See section 6.
Gaseous nickel carbonyl is disposed of by controlled incineration in approved equipment.

14. Transport Information

Classified as a dangerous goods for transport by all regulatory authorities.

INCO DOES NOT TRANSPORT NICKEL CARBONYL OFF SITE

15. Regulatory Information

See sections 2 & 3

16. Other Information

Medical staff should note that this data sheet has been lodged with the following Poisons Information Centres at:

The Welsh National Poisons Unit,
Ward West 5,
Llandough,
Penarth,
Cardiff.
CF6 1XX

Tel. No. 01222 709901

17. Notes and Bibliography

Disclaimer: The information in this Data Sheet is provided in good faith and is accurate to INCO's best knowledge and belief but except as implied by law, no representation or warranty is given in relation to the information and INCO accepts no liability.

1 Short Term Exposure Limit of the Health and Safety Executive in the U.K. in EH40 1997.
2 Toxicity review 19 The toxicity of nickel and its inorganic compounds: Health and safety executive 1987.
3 IPCS Environmental Health Criteria 108 Nickel: WHO Geneva 1991.
4 INCO Clydach Refinery Carbonyl Protocol.

CHLOROFORM DRAFT AEGL VALUES PRESENTATION OVERHEADS

National Advisory Committee for Acute Exposure Guideline Levels

Meeting No. 10
Old Post Office, M09
Washington, D.C.
June 8-10, 1998

DRAFT AEGL VALUES FOR CHLOROFORM					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	68 ppm (331 mg/m^3)	48 ppm (234 mg/m^3)	24 ppm (117 mg/m^3)	17 ppm (83 mg/m^3)	Strong odor detected by human subjects exposed to 680 ppm for 30 min. (Lehmann and Hasegawa, 1910)
AEGL-2	351 ppm (1709 mg/m^3)	248 ppm (1208 mg/m^3)	124 ppm (604 mg/m^3)	88 ppm (429 mg/m^3)	Estimated narcosis threshold; human subjects exposed to 4300 ppm for 20 min. Lehmann and Hasegawa, 1910)
AEGL-3	922 ppm (4491 mg/m^3)	652 ppm (3175 mg/m^3)	326 ppm (1588 mg/m^3)	231 ppm (1223 mg/m^3)	Estimated lethality threshold for rats; 3-fold reduction in 4-hr LC_{50} of 9780 ppm to 3260 ppm (Lundberg et al., 1986)

NONLETHAL TOXICITY OF CHLOROFORM IN HUMANS FOLLOWING ACUTE INHALATION EXPOSURE

No. of subjects	Exposure concentration (ppm)	Exposure duration (min)	Effect	Reference
3	920	3	vertigo	Lehmann and Hasegawa
3	680	30	strong odor	Lehmann and Hasegawa
3	1400	30	light head, lassitude, headache	Lehmann and Hasegawa
3	3000	30	pounding heart, gagging	Lehmann and Hasegawa
NA	4300-5100	20	intoxication, dizziness	Lehmann and Hasegawa
NA	7200	15	intoxication, dizziness	Lehmann and Hasegawa
1502	22,500	<30 - >120 (most <30)	surgical plane anesthesia, cardiac irregularities	Whitaker and Jones, 1965
58	8500-13,000	113 (mean duration)	surgical plane anesthesia	Smith et al., 1973
2	<0.5	330	no effects*	McDonald and Vire, 1992
2	<0.88	150	no effects*	McDonald and Vire, 1992

* Health screening conducted at 5 hours postexposure and at one year after exposure

LETHAL TOXICITY OF CHLOROFORM IN LABORATORY SPECIES FOLLOWING ACUTE INHALATION EXPOSURE

Species	Exposure concentration (ppm)	Exposure duration (min)	Effect	Reference
Rat	9780	240	4-hr LC_{50}†	Lundberg et al., 1986
Rat	3000	240	100% mortality	Haskell Laboratories, 1964
Rat	3700	240	75% mortality*	Haskell Laboratories, 1964
Rat	5000	240	75% mortality*	Haskell Laboratories, 1964
Rat	8000	240	≈80% mortality	Smyth et al., 1962
Rat	"saturated conc."	5	100% mortality	Smyth et al., 1962
Rat	726	720	lethality (no specifics provided)	Puri et al., 1971
Mouse	5529	420	7-hr LC_{30}	von Oettingen et al., 1949
Mouse	5687	420	7-hr LC_{50}	von Oettingen et al., 1949
Mouse	6963	420	7-hr LC_{90}	von Oettingen et al., 1949
Mouse	4,710-5,529	71-175	66% mortality	Fühner, 1923
Mouse	6,758-7,782	35	14% mortality	Fühner, 1923
Mouse	2,458-5,120	48-215	no deaths	Fühner, 1923
Mouse	5,585	120	75% mortality‡	Fühner, 1923
Mouse	4500	560 min	50% lethality (LCt_{50})	Gehring (1968)

† Mortality at 24 hours postexposure * Deaths at 2-3 days postexposure ‡ Deaths at 105-140 minutes postexposure

NONLETHAL TOXICITY OF CHLOROFORM IN LABORATORY SPECIES FOLLOWING ACUTE INHALATION EXPOSURE				
Species	Exposure concentration (ppm)	Exposure duration	Effect	Reference
Rat	500	6 hrs	statistically significant elevation in serum enzyme activity	Wang et al.,1994
Rat	10	6 hrs/day for 7 days	histopathologic changes in the liver	Larson et al. 1994
Rat	50	8 hrs	no increase in liver weight	Ikatsu and Nakajima, 1992
Rat	100	8 hrs	marginal, biologically insignificant increase in serum enzyme activity	Ikatsu and Nakajima, 1992
Rat	153	4 hrs	elevated serum enzyme activity	Lundberg et al., 1986
Rat	292	4 hrs	elevated serum enzyme activity	Brondeau et al. (1983)
Rat	10,000	2 hrs	no effect on hepatic GSH[a]	Brown et al., 1974

[a] Narcosis and significant reduction in GSH was found in phenobarbital-induced rats exposed for 2 hrs to 5,000 ppm chloroform.

NONLETHAL TOXICITY OF CHLOROFORM IN LABORATORY SPECIES FOLLOWING ACUTE INHALATION EXPOSURE (cont.)				
Species	Exposure concentration (ppm)	Exposure duration	Effect	Reference
Mouse	2,458-5,120	48 min	reflex loss	Fühner, 1923
Mouse	100	4 hrs	fatty infiltration of the liver	Kylin et al., 1963
Mouse	693	1 hr	renal toxicity	Deringer et al. (1953)
Mouse	246	2 hrs	renal tubular necrosis	Culliford and Hewitt (1957)
Mouse	665	2 hrs	renal necrosis in males	Culliford and Hewitt (1957)
Mouse	4500	35 min	50% narcosis (ECt_{50})	Gehring (1968)
Mouse	4500	13.5 min	50% significantly[b] elevated SGPT (ECt_{50})	Gehring (1968)
Cat	7500	78 min	light narcosis	Lehmann and Schmidt-Kehl, 1936
Cat	22,000	10 min	narcosis, eye, mouth and nose irritation	Lehmann and Schmidt-Kehl, 1936

[b] Approximately 2.2-fold increase relative to unexposed controls; considered by investigators to be statistically significant.

AEGL-1

- Human Data
  - odor threshold: 133-276 ppm
  - limited data for AEGL-1-specific effects
  - strong odor at 680 ppm for 30 minutes
  - validation of exposure terms ?

- Animal Data
  - limited data pertaining to AEGL-1 effects
  - elevated serum enzyme activity, minor histopathologic findings

AEGL-1

DRAFT AEGL-1 VALUES FOR CHLOROFORM			
30-min	1-hr	4-hr	8-hr
68 ppm [331 mg/m^3]	48 ppm [234 mg/m^3]	24 ppm [117 mg/m^3]	17 ppm [83 mg/m^3]

- **Key study: Lehmann and Hasegawa (1910); strong odor following 30-min exposure to 680 ppm; human subjects**

- **Uncertainty/modifying factors**
  - **3 for intraspecies; minimize sensitive individual response because P-450 induction is not likely to be a critical factor in odor detection response**
  - **modifying factor of 3 for data base quality (e.g., older data that are difficult to verify)**
- ***n* = 2**

AEGL-2

- **Human Data**
  - **exposures indicative of narcosis threshold**
    1400 ppm, 0.5 hr
    3000 ppm, 0.5 hr
    7200 ppm, 0.25 hr
  - **anesthesia data (8500-22,500 ppm, <0.5 - 2 hrs)**

- **Animal data**
  - **renal necrosis and fatty degeneration of the liver**
    246 ppm, 2 hrs
    665 ppm, 1 hr
  - reflex loss, narcosis
    7500 ppm, 78 min
    4500 ppm, 35 min

AEGL-2

DRAFT AEGL-2 VALUES FOR CHLOROFORM			
30-min	1-hr	4-hr	8-hr
351 ppm [1709 mg/m^3]	248 ppm [1209 mg/m^3]	124 ppm [604 mg/m^3]	88 ppm [429 mg/m^3]

- Key study: Lehmann and Hasegawa (1910); dizziness and "intoxication" following 20-min exposure to 4300 ppm; human subjects
- Uncertainty/modifying factors
  - 3 for intraspecies; minimize sensitive individual response because P-450 induction may not be a critical factor for narcosis
  - modifying factor of 3 for data base quality (e.g., difficult to verify exposure terms)
- $n = 2$

AEGL-3

- **No quantitative data in humans**

- **Animal data**
  - **lethality data (LC_{50})**
    4-hr LC_{50} = 9780 ppm (rat)
    7-hr LC_{50} = 5687 ppm (mouse)

- **Data unavailable for calculating *n*; default to *n* = 2**

- Uncertainty factors
  - 3 for intraspecies variability
  - no UF for interspecies variability
- Modifying factor
  - 3 for deficiencies

AEGL-3

DRAFT AEGL-3 VALUES FOR CHLOROFORM			
30-min	1-hr	4-hr	8-hr
922 [4491 mg/m^3]	652 ppm [3175 mg/m^3]	326 ppm [1588 mg/m^3]	231 ppm [1223 mg/m^3]

- Key study: Lundberg et al., 1986; lethality threshold (3,260 ppm) estimated as 1/3 of 4-hr LC_{50} (9780 ppm)
- Uncertainty/modifying factors
  - 3 for intraspecies; minimize sensitive individual response (e.g., P-450 induction; existing liver or renal conditions)
  - modifying factor of 3 for data base quality (e.g., relatively limited data for lethality following inhalation exposure)
- $n = 2$

ISSUES

- overall quality of data
  - validation of exposure terms for human data
  - AEGL-specific endpoints poorly represented by available data

- selection of critical endpoints for AEGL-1 and AEGL-2 derivations are protective (i.e., effect severity are minimal relative to AEGL definition)
  - odor (AEGL-1)
  - conservative estimate of narcosis threshold (AEGL-2)

- uncertainty factors
  - metabolism/disposition differences (rodents>primates)

EMBYROTOXICITY AND FETOTOXICITY OF CHLOROFORM IN RATS FOLLOWING GESTATIONAL EXPOSURE					
Parameter	Control	Pair-fed control	30 ppm	100 ppm	300 ppm
% pregnancy (pregnant/bred)	88 (68/77)	100 (8/8)	71 (22/31)	82 (23/28)	15 (3/20)[b]
corpora lutea/dam	14±2	14±2	16±3[b]	14±2	14±1
live fetuses/litter	10±4	10±4	12±2	11±2	4±7[b]
% reabsorptions/implantations	8(63/769)	7(6/87)	8(24/291)	6(16/278)	61(20/33)[b]
fetal body weight (g)	5.69±0.36	5.19±0.29[b]	5.51±0.20	5.59±0.24	3.42±0.02[b]
fetal crown-rump length (mm)	43.5±1.1	42.1±1.1[b]	42.5±0.6[b]	43.6±0.7	36.9±0.2[b]
total gross anomalies[a]	1/68	0/8	0/30	13/23[b]	0/3
total skeletal anomalies[a]	46/68	3/8	20/22[b]	17/23	2/3
total soft tissue anomalies[a]	33/68	3/8	10/22	15/23	1/3

[a] litters affected/litters examined
[b] Significantly different from control; $p < 0.05$

DEVELOPMENTAL TOXICITY OF CHLOROFORM IN MICE EXPOSED DURING GESTATION						
Parameter	Days 1-7		Days 6-15		Days 8-15	
	Control	100 ppm	Control	100 ppm	Control	100 ppm
Litters examined	22	11	29	12	24	18
Resorptions/litter	2±2	4±5[a]	2±2	1±1	2±2	2±2
Fetal body weight (g)	1.02±0.10	0.92±0.07[a]	0.99±0.11	0.95±0.13	1.00±0.12	0.85±0.17[a]
Fetal crown-rump length	24.7±1.0	23.6±1.2[a]	23.7±1.3	23.2±1.1	24.1±1.1	22.9±2.2[a]
Cleft palate fetuses (litters) affected	3(1)	0	0	0	1(1)	10(4)[a]

[a] Significantly different from control ($p < 0.05$)

DERIVATION OF AEGL VALUES FROM ALTERNATE DATA SETS

Endpoint/rational/reference	30 min	1 hr	4 hrs	8 hrs	Comments
AEGL-1					
Ikatsu and Nakajima (1992): increased serum enzyme activity; rats exposed to 100 ppm for 8 hrs	120 ppm	84 ppm	42 ppm	30 ppm	$n = 2$; UF of 10; 3 for protection of sensitive individuals; MF=3 for data base UF[a]
AEGL-2					
Schwetz et al. (1974): gestational exposure of rats (7 hrs/day, g.d. 6-15) produced embryotoxicity and fetotoxicity	11.1 ppm	27.8 ppm	3.9 ppm	2.7 ppm	$n = 2$; UF of 10; 3 for protection of sensitive individuals; MF=3 for data base
AEGL-3					
von Oettingen et al. (1974): rat 7-hr LC_{50} of 5,687 ppm	708 ppm	501 ppm	252 ppm	177 ppm	3-fold reduction to estimate lethality threshold; $n=2$; UF = 3 for intraspecies; MF = 3 for overall data quality

n = 2 for temporal scaling ($C^n \times t = k$); data unavailable for empirical derivation of n.

[a] UF for interspecies extrapolation not applied; available data indicate that humans metabolize chloroform more slowly than do laboratory species.

CARBON TETRACHLORIDE AEGL

Presentation Overheads - Revisit/Issues of AEGL-3

National Advisory Committee for
Acute Expsoure Guideline Levels for Hazardous Substances

Meeting No. 10
Old Post Office, M09

June 8-10, 1998

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	16 ppm 100.6 mg/m^3	12 ppm 75.5 mg/m^3	6.9 ppm 43.4 mg/m^3	5.2 ppm 32.7 mg/m^3	nervousness, slight nausea in human subjects (Davis, 1934)
AEGL-2	90 ppm 566.1 mg/m^3	68 ppm 427.7 mg/m^3	39 ppm 245.3 mg/m^3	30 ppm 188.7 mg/m^3	nausea, vomiting, headache in human subjects (intolerable to one of four subjects) (Davis 1934)
AEGL-3	230 ppm 1,446.7 mg/m^3	170 ppm 1,069.3 mg/m^3	99 ppm 622.7 mg/m^3	75 ppm 471.8 mg/m^3	estimated lethality threshold (LC_{01} = 5,135.5 ppm) in rats (Adams et al.,1952; EPA-OTS, 1986)

- AEGL-1 and AEGL-2 values used a total uncertainty factor of 10 for protection of sensitive individuals (e.g., consumers of alcohol or those exposed to cytochrome P-450 inducers)

- Temporal extrapolation $C^n \times t = k$, where n= 2.5 based upon animal lethality data.

- For AEGL-3, total uncertainty factor of 30 was applied; 10 for protection of sensitive individuals and 3 for interspecies variability (subchronic animal studies showed that long-term exposures at or above the proposed AEGL-3 values did not result in lethal responses and, therefore, further reduction of the AEGL-3 was not justified).

ISSUE

The AEGL-3 values will not protect some sensitive individuals (e.g., those with ethanol-induced P-450 activity)

- **Norwood et al. (1950): 15-minute exposure to 250 ppm (estimated based on reconstruction of accident) caused death in "heavy drinker"**

  -represents sensitive individual
  -anecdotal
  -reconstructed estimate of exposure concentration
  -dermal exposure ?

- **15-minute AEGL-3 based on current AEGL-3 development criteria would be 299 ppm**

  -no protection for above individual

- **Manno et al. 1996: Individuals with high ethanol consumption (120 and 250 g/day) developed severe hepato- and nephrotoxicity following exposure to CCl_4 from fire extinguisher vapors**

  - non drinkers were unaffected

  - no exposure terms, qualitatively but not quantitatively useful

- **Wang et al. (1997): pretreatment of rats with ethanol (2 g/rat/day for 3 weeks) increased toxicity of 6-hr exposure to carbon tetrachloride**

CCl_4	SGOT (IU/l)	SGPT (IU/l)
0 ppm	29±4	20±5
0 ppm (ethanol)	31±6	18±4
50 ppm	33±5	20±6
50 ppm (ethanol)	62±138* **	41±9* **
500 ppm	57±22*	38±12*
500 ppm (ethanol)	1720±698* **	870±312* **

* significantly different from control at 0 ppm ($p<0.05$)

** significantly different from control exposed to same chemical and concentration ($p<0.05$)

P-450 activity: Control: 0.74 nmol/mg protein; Ethanol: 1.01 nmol/mg protein

- at high exposures (500 ppm) statistically and biologically relevant increase in biochemical index of hepatotoxicity
- no statistical difference in toxicokinetics between ethanol treatment and CCl_4 alone
- no histopathological correlates presented in report
- no lethality data presented in report

- **Ray and Mehendale (1990): ethanol pretreatment (10 mmol/kg) lowered oral LD_{50} of CCl_4 in rats approximately 25%.**

  - statistically significant increase in hepatotoxicity based upon serum enzyme activity and histopathology

  - no significant change in lethality resulting from ethanol pretreatment

  - intraperitoneal route

SUMMARY

- Case reports for humans indicate that individuals with excessive ethanol consumption are severely affected by CCl_4 exposures that have little effect on non-drinkers; quantitative exposure data are, however, limited

- Animal data show that ethanol-induction of cytochrome P-450 significantly increases some indices of CCl_4 hepatotoxicity

- Magnitude of increased lethality resulting from ethanol-CCl_4 interaction uncertain; animal data suggest it to be less than 10-fold

- Norwood et al. case report anecdotal; exposure based on reconstruction estimate; uncertainty regarding concurrent dermal exposure (i.e., anecdotal, equivocal data used as a key study ?)

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 9 Highlights
Old Post Office, M09
1100 Pennsylvania Avenue
Washington, D.C.
March 10-12, 1998

INTRODUCTION

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 8 (December 8-10, 1997) were reviewed and approved as presented (Appendix A).

Dr. George Rusch (Chair) provided brief introductory remarks including the fact that the Standing Operating Procedures (SOP) were of high priority and that Dr. Falke would be presenting an overview of the SOP Working Group efforts later in the meeting. Dr. Morawetz (ICWUC) expressed concerns regarding the AEGL-3 values for carbon tetrachloride and that they may not be protective of alcoholics (Attachment 3). He also circulated a report pertaining to an accident involving the deaths of four workers following exposure to hydrogen cyanide that was generated by the interaction of muriatic acid and zinc cyanide during the cleaning of a vat (Attachment 4).

Dr. Paul Tobin (EPA-DFO) mentioned that plans were being made for a joint meeting with the National Academy of Sciences Committee on Toxicology for the June NAC/AEGL meeting.

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group

Dr. Ernest Falke (EPA) provided a summary of the SOP Working Group efforts. As previously stated by Dr. Garrett (Project Director), the SOP Working Group in addition to interpreting and expanding on the NAS guidelines (NAS, 1993), is documenting approaches used thus far in AEGL development. The SOP document currently addresses three major areas: (1) calculation of AEGL values, (2) format and content of technical support documents, and (3) development of information and data for technical support documents. Efforts pertaining to the first are on-going and include endpoints for AEGL levels as well as guidance for uncertainty factor and modifying factor application, time scaling, scientific rationale, policies for carcinogenic risk, use of NOAELs and LOAELs, and reconstruction modeling. This section also serves as a "living document" to capture approaches used by the NAC/AEGL in their development of AEGL values. The second area establishes format and consistency guidelines for the technical support documents, summary tables, rounding of AEGL values, and multiplication of uncertainty factors. The third major area provides guidance on assessing the quality of available data, and outlines the responsibilities and tasks of the chemical manager, chemical reviewer, and staff scientists developing draft AEGL values.

Federal Register Comments on Interim Draft AEGLs
Dr. Roger Garrett presented an overview of generic comments and issues from the Federal Register comment period (Attachment 5).

In response to the issue of establishing minimum data set guidelines, Dr. Roger Garrett stated that the NAC/AEGL relies on the NAS guidelines[1] (NAS, 1993) as a basis for AEGL development. It was also stated that the NAC/AEGL is captive to data that are available but that a 2/3 majority vote by the NAC/AEGL is required to AEGL values.

Regarding the use of NOAELs and LOAELs, Roger explained that AEGL levels are threshold effect levels. Additionally, attempts have been made and will continue to be made regarding the detailed and complete justification of uncertainty factors and default values in the development of AEGLs.

Some of the comments to the Federal Register notice pertained to definitions. A summary of these issues consistent with the annotation on page 2 of the public comments summary (Attachment 5) is presented below.

1. AEGL level definitions will be defined in more detail. Of special concern in this respect are chemicals that may not elicit AEGL-1 type effects.

2. For AEGL development, asthmatics are routinely considered a major subpopulation and not "hypersusceptible." They are not considered to be idiosyncratic responders.

3. The defining of protected populations was a recurring comment regarding the proposed AEGLs. A more definitive distinction between susceptible and hypersusceptible is required and will be addressed. Dr. Garrett also emphasized that children are routinely considered when developing AEGLs and that this effort is often guided by the presence of a pediatrician on the NAC/AEGL.

4. The fact that human infants <4 months old represent only 0.4% of the population was not a representative sensitive population to be included in AEGL development.

5. As previously noted, a more robust definition of susceptible vs hypersusceptible is considered appropriate. It was proposed that it may be useful to maintain an on-going list of examples pertaining to this issue and ultimately publish a solidification of NAC/AEGL and NAS thoughts on this issue.

6. Although it was originally planned to have a subcommittee of the NAC/AEGL address the issue of susceptible vs hypersusceptible populations, this effort is currently being addressed by the SOP Working Group.

7. Regarding comments that AEGL definitions are obscure and not reflective of customary definitions of health reference levels, it was emphasized that the AEGL definitions currently in place do, in fact, reflect the goals and endpoints that have been set by the NAC/AEGL and are consistent with NAS

[1] NAS (1993). Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances. Committee on Toxicology/National Research Council, National Academy Press, Washington, D.C.

guidelines. Furthermore, as previously stated, AEGLs are not "customary;" by definition, they represent effect/action levels.

8. The comment suggesting that AEGL-1 levels be protective of all potential adverse effects is not consistent with the definition.

Comments were also received regarding the application of uncertainty factors, the use of time scaling, the application of dosimetric adjustments, and the estimation of lethality by adjustment of LC_{50} values. Many of these were chemical-specific. However, general responses were in order for some of these issues. Uncertainty factor application will continue to be justified as thoroughly as possible. When appropriate data are available, time scaling has been based upon empirically derived and chemical specific information. The use of a default time scaling value and its inherent value or limitations is currently being addressed by the SOP Working Group. The application of dosimetric adjustments is also being revisited on a chemical-specific basis, and determination of toxicity thresholds (especially lethality thresholds) is constantly being examined by the NAC/AEGL and SOP Working Group.

Chemical-Specific Issues on Federal Register Proposed AEGLs

Aniline

No revisions or revisit by NAC/AEGL required.

Fluorine

No revisions or revisit by NAC/AEGL required.

Chlorine

In regard to the difference between the ERPG and AEGL values for chlorine, it was stated that the AEGL value places more emphasis on the response of the asthmatic. No revisions or revisit by NAC/AEGL required.

Nitric acid

No revisions or revisit by NAC/AEGL required.

Phosphine

No revisions or revisit by NAC/AEGL required.

Hydrazine

Concern regarding the use of a dosimetric conversion and its impact on the proposed AEGLs require revisiting. Additionally, the use of temporal extrapolation from a 24-hour exposure and the subsequent flat-line AEGL-1 values needs to be reassessed at the next NAC/AEGL meeting.

Methylhydrazine

The proposed AEGL values were originally calculated using an $n = 1$ for temporal scaling. More recently, an n value of 0.80 - 0.84 has been determined empirically from available data. AEGL values recalculated using a midpoint (n=0.82) of the empirically derived values of n resulted in elevated AEGL-2 and 3 values. Because the recalculation represented a more precise and complete use of the available data, the NAC/AEGL approved the revised values (YES:22; NO:1). No additional revisit required (Appendix B).

Original AEGL Values for Methylhydrazine (n=1.0)

AEGL-1	NA	NA	NA	NA
AEGL-2	2 ppm	1 ppm	0.2 ppm	0.1 ppm
AEGL-3	6 ppm	3 ppm	0.7 ppm	0.3 ppm
Revised AEGL Values for Methylhydrazine (n=0.82)				
AEGL-1	NA	NA	NA	NA
AEGL-2	5.2 ppm	2.2 ppm	0.4 ppm	0.18 ppm
AEGL-3	25 ppm	11 ppm	2 ppm	0.86 ppm

1,1-Dimethylhydrazine & 1,2-Dimethylhydrazine

A suggestion was made and approved to include cancer risks of 10^{-5} and 10^{-6} in the carcinogenic risk calculation Appendix. Additionally, a description regarding use of the noncancer endpoint for AEGL development was made (this verbiage is already in the technical support document). No additional revisit required.

1,2-Dichloroethylene

No revisions or revisit by the NAC/AEGL required.

Ethylene oxide

There was concern was regarding the use of data from a dominant lethal study for development of AEGL-2. It was suggested that Judy Strickland EPA-RTP) be invited to address the NAC/AEGL and that ethylene oxide be revisited at the next NAC/AEGL meeting.

Arsine

No revisions or revisit by the NAC/AEGL required.

Review of Proposed AEGLs to be Submitted to Federal Register for Public Comment

A reaffirmation of the second set of proposed draft AEGLs for 11 chemical substances was conducted by the NAC/AEGL. The technical support documents were distributed to NAC/AEGL members for review relative to currently available SOPs. The respective chemical managers for these chemicals provided comments on the current status of these chemicals.

Allyl alcohol	-	no additional comments
Allyl amine	-	no further comments
Ammonia	-	no comments
Boron trichloride	-	no additional comments
Chlorine trifluoride	-	current document and proposed draft AEGLs are consistent with NAC/AEGL procedures and approaches
Diborane	-	current document and proposed draft AEGLs reflect NAC/AEGL deliberations
Ethylenimine	-	current document and proposed draft AEGLs reflect NAC/AEGL deliberations
Hydrogen chloride	-	only editorial adjustments required

Methyl mercaptan	-	rationale for AEGL-1 incorporated as required
2,4 -Toluene diisocyanate	-	one minor comment to be incorporated; no substantial changes
2,6 -Toluene diisocyanate		required for the toluene diisocyanates

General Interest Items

- George Rusch reported that both the German MAK Commission and the Threshold Limit Value Committee of the American Conference of Governmental Industrial Hygienist consider irritation a threshold phenomena independent of exposure duration and that this is consistent with the NAC/AEGL position.
- John Hinz stated that there is a symposium on jet fuels scheduled at Brooks AFB in April, and that the NAC/AEGL deliberations on jet fuels AEGLs be postponed until at least Dec. 1998.
- The response to Federal Register comments should be from the NAC/AEGL proper and not from an individual.

AEGL PRIORITY CHEMICALS

Bromine, CAS No. 7726-95-6

Chemical Manager: Dr. Zarena Post, TX Nat. Resource Conserv. Comm.
Author: Dr. Sylvia Talmage, ORNL

In Dr. Post's absence, Dr. Larry Gephart (Exxon Biomedical) served as chemical manager for bromine. An overview of the limited data was provided by Dr. Sylvia Talmage (Attachment 6). Sylvia noted that the data was difficult to interpret with respect to application to AEGL development. Following a brief discussion, it was the consensus of the NAC/AEGL that a request be made to industry to conduct an RD_{50} (Respiratory Depression) study and also to obtain an LC_{50} in a species other than the mouse rather than proceeding with AEGL development. The development of AEGL values for bromine will be tabled pending results of the research inquiry. An assessment of the research feasibility or possibility of obtaining more data will be presented at the June meeting, at which time a decision will be made whether or not to proceed with the limited available data.

Action Item: Larry Gephart and Steve Barbee were asked to check into industrial sponsorship regarding research needs consistent with developing AEGL values. A status report was requested for the next NAC/AEGL meeting.

Nitric oxide, CAS No.10102-43-9

Chemical Manager: Dr. Loren Koller, Oregon State Univ.
Author: Dr. Carol Forsyth, ORNL

Dr. Carol Forsyth reviewed the limited data for nitric oxide (Attachment 7) explaining that additional data consistent with AEGL development needs were presented at the recent Society of Toxicology meeting. These data have been requested. Data were limited to developing only AEGL-1 values; 80 ppm for all time points based upon methemoglobin formation and no uncertainty factors. Discussion proceeded and revolved around the conversion of nitric oxide to nitrogen dioxide under ambient conditions, and the fact that off-site

populations may be exposed to that latter. Debate ensued regarding the relevance of NO vs NO_2 AEGLs and the need for AEGLs for NO, NO_2, or both. Concern was also expressed regarding the validity of 4- and 8-hour values for NO. Dr. Borak stated that the methemoglobin formation is a marker of exposure and that individuals exposed during accidental releases would likely experience NO_2-induced respiratory tract irritation prior to health-impairing methemoglobin formation. It was the consensus of the NAC that AEGLs be developed for NO but that they be held in abeyance until data on NO_2 can be examined. AEGL values for NO_2 will be derived for comparison to NO. Both chemicals will be then addressed.

Action Item: Paul Tobin will check with NASA regarding potential for N_2O_4 AEGL development.

Chloromethyl methyl ether, CAS No. 107-30-2

Chemical Manager: Dr. Ernest Falke, EPA
Author: Dr. Sylvia Milanez, ORNL

Dr. Falke presented a summary of the major issue regarding chloromethyl methyl ether (CMME) and Dr. Sylvia Milanez provided an overview (Attachment 8) of the available data and development of the AEGLs. A major point of discussion focused on the carcinogenic potential of this chemical, specifically an analog that is virtually always present as a contaminant. A 10^{-4} cancer risk was calculated for CMME. Discussion ensued regarding the selection of the cancer risk level of concern. Generally, the majority of NAC members believed that the 10^{-4} risk was appropriate for a once-in-a-lifetime exposure and to avoid creating an atmosphere of anxiety regarding potential cancer risk in light of deficient data. A poll of the NAC indicated that, based upon available data, it was more appropriate to develop AEGL values based upon noncancer toxicity. A motion was made by Dr. George Rodgers (seconded by Dr. Loren Koller) to accept the draft AEGL values as presented in the TSD. The motion carried (YES:23; NO:0; ABSTAIN:0 for AEGL-1 and AEGL-3; YES:21; NO:2; ABSTAIN:0 for AEGL-2) (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR CHLOROMETHYL METHYL ETHER

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	ND	ND	ND	ND	No studies available
AEGL-2	0.12 ppm (0.38 mg/m^3)	0.082 ppm (0.27 mg/m^3)	0.041 ppm (0.13 mg/m^3)	0.029 ppm (0.095 mg/m^3)	tracheal/bronchial squamous metaplasia; regenerative hyperplasia
AEGL-3	1.8 ppm (6.1 mg/m^3)	1.3 ppm (4.3 mg/m^3)	0.65 ppm (2.1 mg/m^3)	0.46 ppm (1.5 mg/m^3)	7-hr LC_{01} in rats

ND: no data

Action item: As a result of the discussion regarding cancer risk for CMME, it was decided that the subject be addressed in a short issue paper to be attached as an appendix to the technical support document. Dr. Richard Thomas agreed to prepare a brief issue paper as an initial effort regarding the application of carcinogenic risk to AEGL development.

Dimethyldichlorosilane, CAS No. 75-78-5
Methyltrichlorosilane, CAS No. 75-79-6

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL

Dr. Cheryl Bast reviewed the data for these chemicals and provided new 1-hour rat lethality data for dimethyldichlorosilane received from Dow Corning Corporation (Attachment 9). Chemical-specific data were unavailable for AEGL-1 and, therefore, the values were developed by analogy to HCl (degradation of dimethyldichlorosilane will yield 2 moles of HCl). Dr. Bast stated that an industry representative explained that although some anecdotal information suggest that the toxicity of some chlorosilanes may differ from that of HCl, newer data suggest that the toxicity of commercial chlorosilanes is similar to that of HCl. Assuming maximum degradation to HCl and equivalent sensitivity of exercising asthmatics (the endpoint used for the HCl AEGL-1 values), the AEGL-1 for dimethyldichlorosilane for all time points was proposed as one half the HCl values (0.9 ppm). The motion to accept these values (made by Dr. David Belluck and seconded by Dr. Thomas Hornshaw) passed unanimously (YES:17; NO:0; ABSTAIN:0). The AEGL-2 values (26 ppm, 13 ppm, 3.3 ppm, and 1.6 ppm for the 30 min. 1, 4, and 8-hour time points) were based upon a 1-hr exposure concentration of 1,309 ppm, a total uncertainty of 100 (10 for interspecies variability, 3 for individual variability, and a data base modifying factor of 3), and $n = 1$. A motion made by Dr. George Rodgers and seconded by Dr. David Belluck passed unanimously (YES:17; NO: 0; ABSTAIN:0). The AEGL-3 values (106 ppm, 53 ppm, 13 ppm, 6.6 ppm for the 30-min, 1, 4, and 8-hour periods) were based upon an estimated lethality threshold and incorporated an uncertainty factor of 30, and $n = 1$. A motion by Dr. Hornshaw (seconded by Dr. Belluck) to accept these values passed unanimously (YES:17; NO:0; ABSTAIN:0) (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	0.9 ppm (4.8 mg/m^3)	Two-fold reduction of the HCl AEGL-1 which was based upon no effect level in exercising asthmatics
AEGL-2	26 ppm (140 mg/m^3)	13 ppm (69 mg/m^3)	3.3 ppm (18 mg/m^3)	1.6 ppm (8.5 mg/m^3)	Corneal opacities; grey spots on lungs of rats (1309 ppm, 1 hr)
AEGL-3	106 ppm (562 mg/m^3)	53 ppm (281 mg/m^3)	13 ppm (69 mg/m^3)	6.6 ppm (35 mg/m^3)	Lethality threshold in rats (1590 ppm, 1 hr)

Dr. Bast presented the data and draft AEGL derivations for methyltrichlorosilane (Attachment 10). Similar to the dimethydichlorosilane, the AEGL-1 was based on analogy to the HCl AEGL-1 and the degradation of the methyltrichlorosilane to 3 moles of HCl. A motion to accept 0.6 ppm as the AEGL-1 for all time points was made by Dr. Hornshaw, seconded by Dr. Steven Barbee, and passed unanimously (YES:17; NO:0; ABSTAIN:0). The AEGL-2 values were based upon ocular opacities in rats exposed for 1 hour to 622 ppm. Using a total uncertainty factor of 30, and n=1, the resulting AEGL-2 values of 12, 6.2, 1.6, and 0.78 ppm

were accepted unanimously (motion made by Dr. Rodgers and seconded by Dr. Niemeier); (vote: YES:17; NO:0; ABSTAIN:0). Following discussions regarding the value of *n* for temporal extrapolation and uncertainty factor application and a by Dr. Rodgers (seconded by Dr. Barbee), the AEGL-3 values of 56, 28, 7, and 3.5 ppm (*n*=1, UF = 30) were unanimously accepted (YES:17; NO:0; ABSTAIN:0) (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR METHYLTRICHLOROSILANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	0.6 ppm (3.7 mg/m^3)	Three-fold reduction of the HCl AEGL-1 which was based upon a no-effect level in exercising asthmatics
AEGL-2	12 ppm (73 mg/m^3)	6.2 ppm (38 mg/m^3)	1.6 ppm (9.8 mg/m^3)	0.78 ppm (4.8 mg/m^3)	Ocular opacities in rats exposed for 1 hour to 622 ppm
AEGL-3	56 ppm 342 mg/m^3)	28 ppm (171 mg/m^3)	7 ppm (43 mg/m^3)	3.5 ppm (21 mg/m^3)	Lethality threshold in rats (1-hr) of 844 ppm

Epichlorohydrin, CAS No. 106-89-8

Chemical Manager: Dr. Richard Thomas, ICEH
Author: Dr. Kowetha Davidson, ORNL

Dr. Richard Thomas presented a brief introduction (Attachment 11) followed by an overview of the data and development of the draft AEGLs by Dr. Davidson (Attachment 12). Lynn Harris of the Technical Affairs Office, Society of Plastics Industry, Inc. was also in attendance as an observer. Concerns were discussed regarding the AEGL-1 uncertainty factor application and variability in the irritation response observed for epichlorohydrin. Although the reported odor threshold for epichlorohydrin ranges from 0.08 to 20 ppm (recognition at 20 ppm) and irritation is known to occur at >10 ppm, it was the consensus of the NAC that 5 ppm be considered for all AEGL-1 time points and that this would represent a protective estimate of the irritation threshold. The NAC noted that this may be a subthreshold for odor perception. A motion was made by Larry Gephart (seconded by Dr. Loren Koller) to accept the 5 ppm values. The motion carried (YES:21; NO:1; ABSTAIN:0). For the AEGL-3, initial discussions focused on the uncertainty factor application and whether or not the 8-hour AEGL-3 value should be developed independently of the other time frames (the 8-hr values [19 ppm] developed from the key studies would be inconsistent with the definition of AEGL-3). The 8-hr AEGL-3 was developed from a study showing that long-term exposures to 30 ppm did not result in shortening of life. A motion was made (Dr. Borak; seconded by Dr. Belluck) and carried to accept AEGL-3 values of 160 ppm, 72 ppm, and 43 ppm for the 30-min, 1-hour, and 4-hour time points (YES:17; NO:2; ABSTAIN:2). Following discussions on developing the 8-hour AEGL-3 value using data from a long-term study, the 8-hour AEGL of 30 ppm was considered to be protective of life-threatening effects following an 8-hour exposure and was accepted (motion by Dr. Borak, seconded by Dr. Belluck; YES:14; NO:1; ABSTAIN:5). For the development of AEGL-2 values, there were discussions regarding identification of an appropriate endpoint. There was extensive discussion on the draft proposed AEGL-2 values from the TSD which were based upon irritation (burning eyes). Although AEGL values for irritation are usually flat-lined, this was not considered desirable for the AEGL-2. Some committee members also expressed concerns about using this endpoint for AEGL-2 values. Ultimately, it was the consensus of the NAC that the AEGL-2 values

be derived by a 3-fold reduction in the AEGL-3 value and that this would be protective of pulmonary edema observed in animal lethality studies. A motion to accept this rationale and consequent values (53 ppm, 24, pp, 16, ppm and 10 ppm) was made by Dr. George Rodgers and seconded by Dr. Niemeier. The motion passed (YES:16; NO:2; ABSTAIN:1) (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR EPICHLOROHYDRIN					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	5 ppm ($18.9\ mg/m^3$)	5 ppm ($18.9\ mg/m^3$)	5 ppm ($18.9\ mg/m^3$)	5 ppm ($18.9\ mg/m^3$)	Odor irritation threshold
AEGL-2	53 ppm ($200.3\ mg/m^3$)	24 ppm ($90.7\ mg/m^3$)	16 ppm ($60.5\ mg/m^3$)	10 ppm ($37.8\ mg/m^3$)	3-fold reduction in AEGL-3 values to protect against pulmonary edema
AEGL-3	160 ppm ($604.8\ mg/m^3$)	72 ppm ($272.2\ mg/m^3$)	43 ppm ($162.5\ mg/m^3$)	30 ppm ($113.4\ mg/m^3$)	Lethality threshold

Nickel carbonyl, CAS No. 13463-39-3

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Robert Young, ORNL

Dr. Blackman opened the presentation by discussing unique physicochemical properties (e.g., degradation properties, dissociation rates, etc.) of nickel carbonyl, especially those that would impact on exposures resulting from accidental releases of the chemical (Attachment 13). Dr. Young presented an overview of the data, emphasized that data were limited to lethality and developmental studies (Attachment 14). He explained that application of a full complement of uncertainty factors (i.e, 10 x 10) as used in the draft AEGLs may be inappropriate due to the fact that LC_{50} data for four species appeared to suggest that larger species were less sensitive. No data were available that were consistent with AEGL-1 endpoints. Furthermore, the toxicity and latency period associated with nickel carbonyl exposures (human case reports often indicated severe or lethal toxic responses hours to days after an initial exposure) are of concern. Two developmental toxicity studies were available from two studies (rat and hamster) that could possibly be used as drivers for AEGL-2 values but would be relationally inconsistent with AEGL-3 values derived using the full complement of uncertainty factors. Following a brief discussion, it was the consensus of the NAC that the AEGL-3 be derived using an estimate of the lethality threshold (LC_{01} of 3.17 ppm) in the most sensitive species (mouse), a total uncertainty factor of 10 (3 for interspecies variability and 3 for intraspecies variability), and default of $n = 2$. The motion to accept the AEGL-3 values of 0.32 ppm, 0.22 ppm, 0.11 ppm, and 0.08 ppm (made by Dr. McClanahan; seconded by Larry Gephart) carried (YES:13; NO:2; ABSTAIN:2) (Appendix G). Due to the lack of additional time, further deliberations and discussions regarding the development of an AEGL-2 based upon the developmental toxicity data in animals, and the status of AEGL-1 were tabled until the next meeting.

SUMMARY OF PROPOSED AEGL VALUES FOR NICKEL CARBONYL					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint

AEGL-1	-	-	-	-	
AEGL-2	-	-	-	-	
AEGL-3	0.32 ppm	0.22 ppm	0.11 ppm	0.08 ppm	Estimated lethality threshold (LC_{01} of 3.17 ppm) in mice, UF=10; *n*=2

ADMINISTRATIVE ISSUES

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

June 8-10, 1998, Washington, D.C.; possible joint meeting the COT
September 14-16, 1998, Oak Ridge, TN

Prepared by: Drs. Robert Young and P.Y. Lu, Oak Ridge National Laboratory, Oak Ridge, TN

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC Meeting No. 9 Agenda
2. NAC Meeting No. 9 Attendee List
3. Information provided by John Morawetz
4. Information provided by John Morawetz
5. Public comments for proposed draft AEGL values
6. Data analysis of Bromine - Sylvia Talmage
7. Data analysis of Nitric oxide - Carol Forsyth
8. Data analysis of Chloromethyl methyl ether - Sylvia Milanez
9. Data analysis of Dimethyldichlorosilane - Cheryl Bast
10. Data analysis of Methyltrichlorosilane - Cheryl Bast
11. Overview of Epichlorohydrin - Richard Thomas
12. Data analysis of Epichlorohydrin - Kowetha Davidson
13. Overview of Nickel carbonyl - Kyle Blackman
14. Data analysis of Nickel carbonyl - Robert Young

LIST OF APPENDICES

A. Approved NAC-8 Meeting Highlights
B. Ballot for Methylhydrazine
C. Ballot for Chloromethyl methylether
D. Ballot for Dichlorodimethylsilane
E. Ballot for Methyl trichlorosilene
F. Ballot for Epichlorohydrin
G. Ballot for Nickel carbonyl

Jun Appendix B

CHO

Date of AEGL NAC meeting: 6/9/98 **Chemical:** ACROLEIN 107-02-8

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	Y	N	Y	Loren Koller	A	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	A	A	A
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	N	Y	John S. Morawetz	Y	N	A
Robert Benson	Y	Y	Y	Deirdre L. Murphy			
Kyle Blackman	A	A	A	Richard W. Niemeier	Y	N	Y
Jonathan Borak	Y	Y	Y	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	Y	N	Y
Luz Claudio	Y	Y	Y	George Rodgers	Y	N	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	N	Y	Bob Snyder	Y	Y	Y
Larry Gephart	Y	Y	Y	Thomas J. Sobotka	Y	N	Y
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Patricia Ann Talcott	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Benjamin A. Jackson	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
Nancy K. Kim	A	A	A				
				TALLY	27/27	20/28	27/27

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.03 ,( )	0.03 ,( )	0.03 ,( )	0.03 ,( )
AEGL 2	0.18 ,( )	0.10 ,( )	0.10 ,( )	0.10 ,( )
AEGL 3	2.5 ,( )	1.4 ,( )	0.48 ,( )	0.27 ,( )

AEGL 1 Motion: Benson **Second:** Thomas

AEGL 2 Motion: Barbee **Second:** Koller

AEGL 3 Motion: Benson **Second:** Rodgers

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/9/98

79-21-0 Appendix C

Date of AEGL NAC meeting: 6/9/98 **Chemical:** CH_3COOH (PERACETIC ACID MIXT)

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	Y	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	A
Robert Benson	Y	Y	Y
Kyle Blackman	A	A	A
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
Luz Claudio	Y	Y	Y
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	A	A	A
Jim Holler	Y	A	Y
Thomas C. Hornshaw	Y	Y	Y
Benjamin A. Jackson	Y	Y	Y
Nancy K. Kim	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	A	A	Y
Glenn Leach	A	A	A
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	N	Y	Y
Deirdre L. Murphy			
Richard W. Niemeier	Y	Y	Y
William Pepelko	A	A	A
Zarena Post	N	Y	Y
George Rodgers	Y	Y	Y
George Rusch, Chair	Y	Y	Y
Bob Snyder	Y	Y	Y
Thomas J. Sobotka	Y	A	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Y	Y	Y
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	A N	A N	A N
TALLY	21/25	22/23	24/25

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.17 ,( )	0.17 ,( )	0.17 ,( )	0.17 ,( )
AEGL 2	0.50 ,( )	0.50 ,( )	0.50 ,( )	0.50 ,( )
AEGL 3	9.6 ,( )	4.8 ,( )	2.6 ,( )	1.9 ,( )

n = 2.2

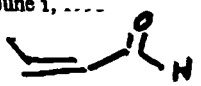
AEGL 1 Motion: Gephart **Second:** Hornshaw

AEGL 2 Motion: Snyder **Second:** Rodgers

AEGL 3 Motion: Falke **Second:** Rodgers

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/9/98

4170-30-3 (cis + trans) June 1, ...
123-73-9 (trans)



Date of AEGL NAC meeting: 6/9/98 **Chemical:** CROTONALDEHYDE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	Y	N	Y	Loren Koller	A	A	A
Steven Barbee	Y	Y	Y	Glenn Leach	A	A	A
Lynn Beasley	A	A	A	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	Y	N	Y
Robert Benson	Y	Y	Y	Deirdre L. Murphy			
Kyle Blackman	A	A	A	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	A	A	A	William Pepelko	A	A	A
William Bress	Y	Y	N	Zarena Post	Y	Y	Y
Luz Claudio	A	A	A	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	A	Y	Bob Snyder	Y	Y	Y
Larry Gephart	Y	Y	P	Thomas J. Sobotka	Y	A	A
John Hinz	A	A	A	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Patricia Ann Talcott	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Benjamin A. Jackson	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
Nancy K. Kim	A	A	A				
				TALLY	23/23	19/21	20/21

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.19 ,( )	0.19 ,( )	0.19 ,( )	0.19 ,( )
AEGL 2	6.9 ,( )	4.4 ,( )	1.1 ,( )	0.56 ,( )
AEGL 3	~~26~~ 27 ,( )	~~13~~ 14 ,( )	2.6 ,( )	1.5 ,( )

AEGL 1 Motion: Benson **Second:** Niemeier

AEGL 2 Motion: Hansen **Second:** Hornshaw

AEGL 3 Motion: Falke **Second:** ~~Thomas~~ Belluck

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/9/98

Appendix E

13463-39-3

Date of AEGL NAC meeting: 6/9/98 **Chemical:** Nickel Carbonyl $Ni(CO)_4$

NAC Member	AEGL 1	AEGL 2	AEGL 3 N/A for 8 hrs	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff		Y		Loren Koller		Y	Y
Steven Barbee		Y	Y	Glenn Leach		A	A
Lynn Beasley		Y	Y	Mark A. McClanahan		N	Y
David Belluck		Y	Y	John S. Morawetz		Y	Y
Robert Benson		Y	N	Deirdre L. Murphy			
Kyle Blackman		Y	Y	Richard W. Niemeier		Y	Y
Jonathan Borak		P	Y	William Pepelko		Y	Y
William Bress		Y	Y	Zarena Post		N	Y
Luz Claudio		Y	Y	George Rodgers		Y	Y
George Cushmac		Y	Y	George Rusch, Chair		Y	Y
Ernest Falke		Y	Y	Bob Snyder		Y	Y
Larry Gephart		P	Y	Thomas J. Sobotka		N	Y
John Hinz		A	A	Kenneth Still		Y	Y
Jim Holler		Y	Y	Patricia Ann Talcott		N	P
Thomas C. Hornshaw		N	Y	Richard Thomas		Y	Y
Benjamin A. Jackson		Y	Y	Thomas Tuccinardi/ Doan Hansen		A N	A P
Nancy K. Kim		A	A				
				TALLY		8/27	25/26

Note N/A 6/15/98

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	0.059 ,( )	0.042 ,( )	0.021 ,( )	N/A ,( )
AEGL 3	0.32 ,( )	0.22 ,( )	0.11 ,( )	N/A ,( )

AEGL 1 Motion: _____ **Second:** _____

AEGL 2 Motion: Alexeeff **Second:** Bress

AEGL 3 Motion: Thomas **Second:** Belluck

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/9/98

Appendix F

67-66-3

Date of AEGL NAC meeting: **Chemical:** $CHCl_3$ CHLOROFORM

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	N	Y
Steven Barbee	N	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	N
Kyle Blackman	A	A	A
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
Luz Claudio	Y	Y	Y
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	A	A	A
Jim Holler	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y
Benjamin A. Jackson	Y	Y	Y
Nancy K. Kim	A	A	A

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	N	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	N	Y
John S. Morawetz	Y	Y	Y
Deirdre L. Murphy			
Richard W. Niemeier	N	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	Y	Y	Y
George Rodgers	Y	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	A
Thomas J. Sobotka	A	A	A
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	Y	Y	Y
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
TALLY	20/23	20/23	22/23

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	N/A ,( )	N/A ,( )	N/A ,( )	N/A ,( )
AEGL 2	390 ,( )	260 ,( )	130 ,( )	94 ,( )
AEGL 3	920 ,( )	650 ,( )	330 ,( )	230 ,( )

AEGL 1 Motion: Belluck / Gephart / Koller **Second:** Thomas / Thomas

AEGL 2 Motion: ~~Koller~~ **Second:** ~~Barbee~~

AEGL 3 Motion: Barbee **Second:** Rodgers

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/10/98